약학박사학위논문

Asymmetric Total Synthesis of (+)-(3*E*)-Pinnatifidenyne and Studies Toward the Syntheses of *trans*-Rhodophytin and (-)-(3*Z*)-Venustinene

(+)-(3*E*)-Pinnatifidenyne의 입체 선택적 전합성 및 *trans*-Rhodophytin과 (-)-(3*Z*)-Venustinene의 전합성에 관한 연구

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Abstract

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The marine genus *Laurencia* of red alga have produced a diverse subset of medium-sized cyclic haloethers containing one or more halogen atoms, diverse stereogenic centers and different lengths of side chains. Since the (+)-Laurencin was reported by T. Irie and co-workers in 1965, which was first isolated medium oxacycle natural product from *Laurencia* species, numerous medium-ring ethers marine natural products have been reported in recent years. Although these secondary metabolites have received significant attention from the synthetic community due to their unique structural features and the biological activities, the construction of the oxacycle skeleton, particularly the eight-membered cyclic ether with side chains, is still formidable task because of their enthalpic and entropic penalties.

Herein, we report the asymmetric total synthesis of (+)-(3*E*)-Pinnatifidenyne (**6**) based our unified synthetic strategy. The key features of our synthesis involve the efficient construction of the *cis*-α,α'-disubstituted oxocene skeleton by highly regioselective intramolecular Tsuji-Trost allylic alkylation, the sequential *in situ* deconjugative isomerization and the elaboration of the crucial chloride functionality mediated by the substrate-controlled diastereoselective reduction. In the present study, we efficiently synthesized the precursor for Pd(0)-catalyzed cyclization *via* Lewis acid-mediated epoxide opening reaction as the convergent synthetic strategy and we envision our unified synthetic strategy can widely apply to more complicated and unique oxocene natural products from *Laurencia* species.

Keywords : medium-sized cyclic haloethers, *Laurencia* species, Pinnatifidenyne, *cis*-α,α'-disubstituted oxocene, intramolecular Tsuji-Trost allylic alkylation, deconjugative isomerization

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Abbreviations

BTMG: 2-*tert*-Butyl-1,1,3,3-tetramethylguanidine

CBS: Corey-Bakshi-Shibata

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DDQ: 2,3-Dichloro-5,6-dicyano-p-benzoquinone

DEAD: Diethyl azodicarboxylate

DHP: Dihydropyran

DIBAL-H: Diisobutylaluminum hydride

DIPEA: *N*,*N*-Diisopropylethylamine

DMAP: *N*,*N*-Dimethylaminopyridine

DMF: *N*,*N*-Dimethylformamide

DMP: Dess-Martin periodinane

DMSO: Dimethyl sulfoxide

DMVS: Dimethylvinylsilyl

Dppb: 1,4-Bis(diphenylphosphino)butane

Dppe: 1,2-Bis(diphenylphosphino)ethane

Dppf: 1,1'-Bis(diphenylphosphino)ferrocene

Dppm: 1,2-Bis(diphenylphosphino)methane

IAEA: Intramolecular amide enolate alkylation

LAH: Lithium aluminum hydride

LDA: Lithium diisopropylamide

LiHMDS: Lithium bis(trimethylsilyl)amide

LPO: Lactoperoxidase

Mc: Chloromethanesulfonyl

MEM: Methoxyethoxymethyl

Ms: Methanesulfonyl

MS: Molecular sieves

NBS: *N*-bromosuccinimide

NCS: *N*-chlorosuccinimide

NMO: *N*-methylmorpholie *N*-oxide

NR: No reaction

PCC: Pyridinium chlorochromate

PMB: *p*-Methoxybenzyl

PPTS: Pyridinium *p*-toluenesulfonate

PTSA: *p*-Toluenesulfonic acid

RCM: Ring-closing metathesis

TBAF: Tetrabutylammonium fluoride

TBCO: Tetrabromocyclohexadienone

TBDPS: *t*-Butyldiphenylsilyl

TBS: *t*-Butyldimethylsilyl

TEA: Triethylamine

TES: Triethylsilyl

Tf: Trifluoromethanesulfonyl

THF: Tetrahydrofuran

THP: Tetrahydropyran

TMS: Trimethylsilyl

TPAP: Tetrapropylammonium perruthenate

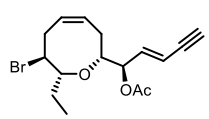
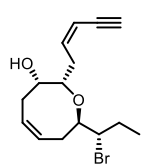
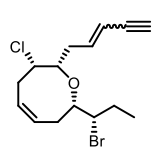
Ts: *p*-Toluenesulfonyl

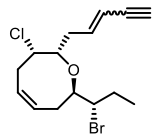
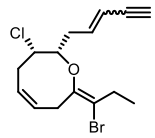
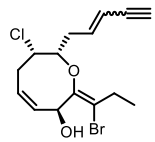
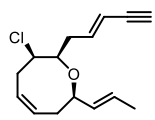
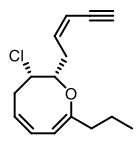
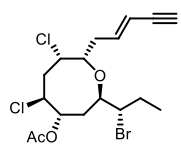
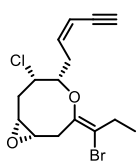
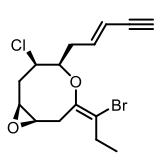
I. Introduction

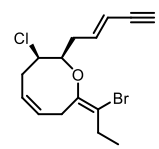
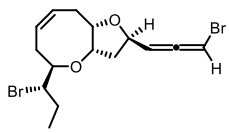
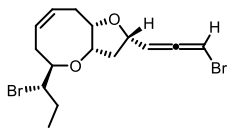
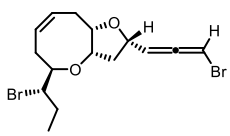
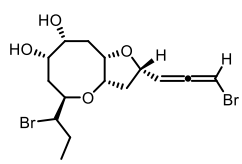
1. C_{15} Medium-Sized Cyclic Haloethers from *Laurencia* Species

The marine genus *Laurencia* of red alga have produced a diverse subset of medium-sized cyclic haloethers. Since the (+)-Laurencin was reported by T. Irie and co-workers in 1965,[1] which was first isolated medium oxacycle natural product from *Laurencia* species, numerous marine natural products containing the medium-ring ethers have been reported in recent years.[2] These cyclic haloethers typically contain one or more halogen atoms, diverse stereogenic centers and different lengths of side chains such as ethyl, propyl, enyne or allene units. The representative medium oxacycle natural products are shown in **Table 1**.

Table 1. C_{15} medium-sized cyclic haloethers from *Laurencia* species

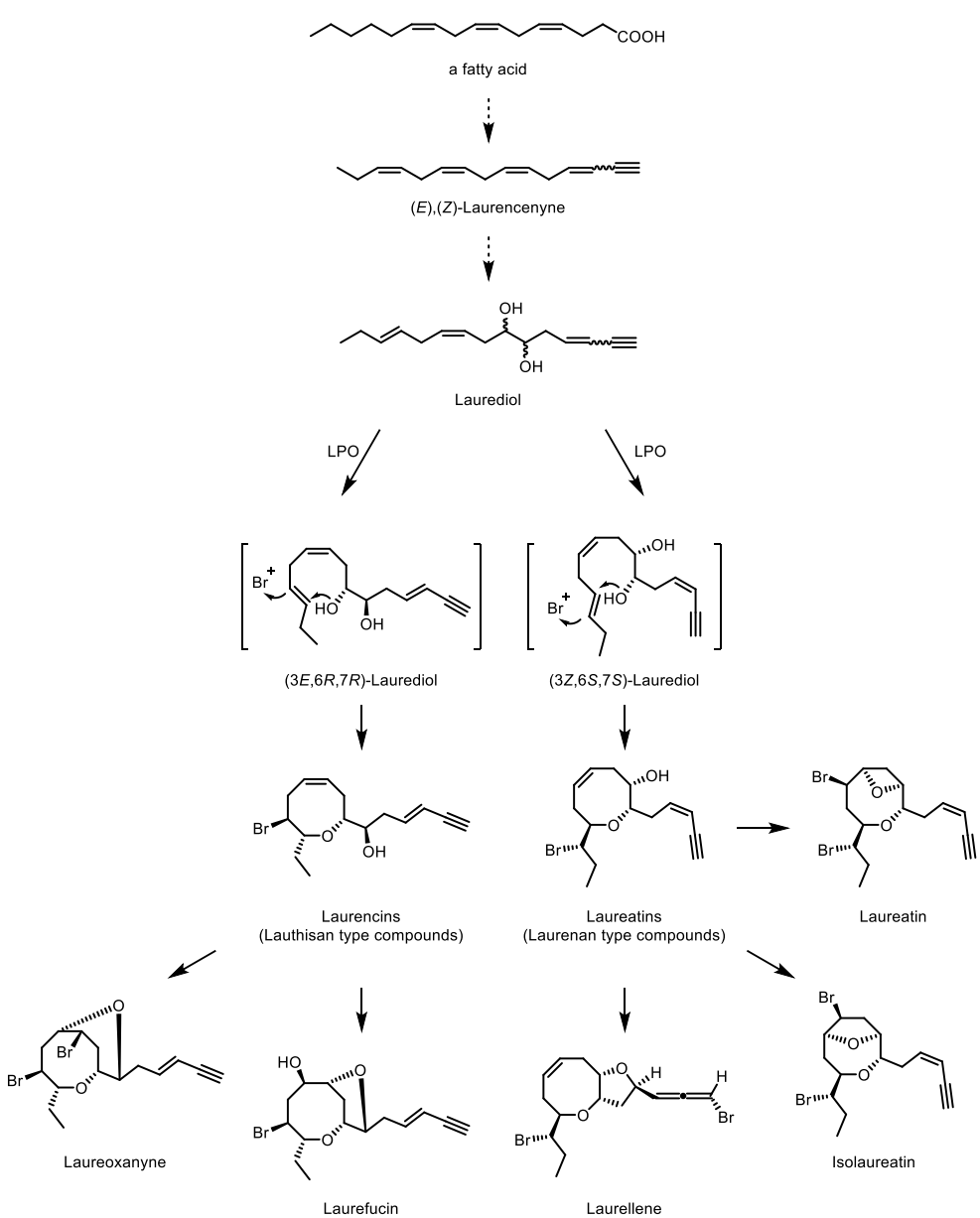
Structure	Common name	Sources	Collection sites
	Laurencin	*L. glandulifera*	Oshoro Bay, Hokkaido, Japan
	Prelaureatin	*L. nipponnoca*	Duwa, Sri Lanka
	(*E*),(*Z*)-Pinnatifidenyne	*L. pinnatifida*	Los Cristianos, Tenerife, Spain

	(*E*),(*Z*)-Dihydrorhodophytin	*L. pinnatifida*	Tenerife, Canary Islands, Spain
	(*E*),(*Z*)-Rhodophytin	*Laurencia* sp.	Guaymas, Mexico
	(*E*),(*Z*)-Chondriol	*Laurencia* sp.	Guaymas, Mexico
	Laurenyne	*L. obtusa*	Aegean Sea, Greece
	(3*Z*)-Venustinene	*L. venusta*	Aomori Prefecture, Japan
	Laurencienyne	*L. obtusa*	Castelluccio, Sicily Island, Italy
	Epoxyrhodophytin	*Laurencia* sp.	Coyote Bay, Japan
	Venustin A	*L. venusta*	Hakodate Bay, Hokkaido, Japan

	Venustin B	*L. venusta*	Hakodate Bay, Hokkaido, Japan
	Laurallene	*L. nipponica*	Oshoro Bay, Hokkaido, Japan
	Pannosallene	*L. pannosa*	Phu Quoc Island, Vietnam
	Nipponallene	*L. nipponica*	Troitsa Bay, Japan
	Laurendecumallene B	*L. decumbens*	Weizhou Island, China

The proposed biogenetic pathways of the eight-membered cyclic haloethers from *Laurencia* species are illustrated in **Scheme 1**.[3] These marine natural products are classified into Laurencins (Lauthisan type compounds) and Laureatins (Laurenan type compounds), which are expected to arise from a fatty acid *via* (*E*),(*Z*)-Laurencenyne and Laurediol. The Lactoperoxidase (LPO) in the presence of the enzymatically-generated bromo cation (Br^+) converted Laurediols into Laurencins and Laureatins by the bromo etherification, which are consumed to be a precursor of Laureoxanyne, Laurefucin, Laureatin, Isolaureatin and Laurellene.

Scheme 1. Proposed biogenetic pathways on *Laurencia* species



Although these halogenated secondary metabolites have received significant attention from the synthetic community due to their unique structural features and the biological activities, the construction of the oxacycle skeleton, particularly the eight-membered cyclic

ether with side chains, is still formidable task because of their enthalpic and entropic penalties.[4]

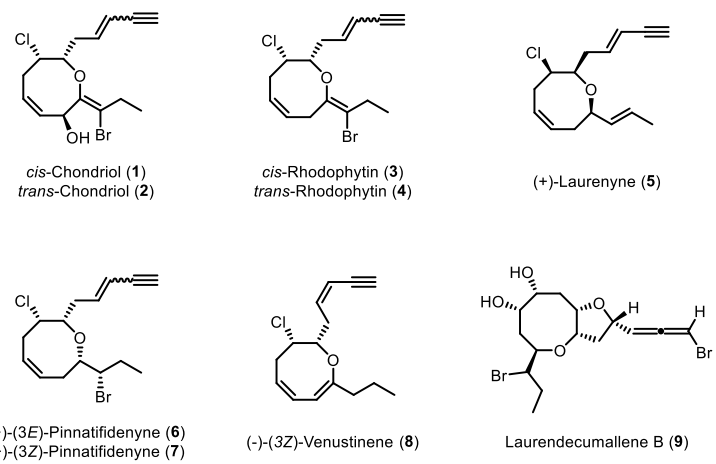
2. Pinnatifidenyne and Other Laurenan Type of Natural Products

Since the isolation of *cis*-Chondriol (**1**) and *trans*-Chondriol (**2**) from the red alga *Laurencia* species reported by W. Fenical and co-workers in 1973, various Laurenan type of metabolites have been isolated from *Laurencia* species in recent years (**Figure 1**).[5]

cis-Rhodophytin (**3**) and *trans*-Rhodophytin (**4**) were also isolated from *Laurencia* species by W. Fenical in 1974.[6] The reassignment of structures for Chondriol and Rhodophytin containing a oxocene skeleton with specific *exo*-vinyl bromide group were reported in 1974 and 1980.[7] (+)-Laurenyne (**5**), containing a oxocene skeleton with α-propenyl and α'-pentenyl side chains, was isolated from *Laurencia obtusa* by R. H. Thomson and co-workers in 1980.[8] In 1988, the first total synthesis of (**5**) was reported by L. E. Overman and co-workers.[9] The absolute configuration was revised in this work and confirmed by the second total synthesis, which was reported by R. K. Boeckman and co-workers in 2002.[10]

(+)-(3*E*)-Pinnatifidenyne (**6**) and (+)-(3*Z*)-Pinnatifidenyne (**7**), a C_{15} halogenated acetylenic cyclic ether, were isolated from *Laurencia pinnatifida* by A. G. González and co-workers in 1982 and its absolute configuration was reassigned in 1991 on the basis of X-ray diffraction analysis.[11] Pinnatifidenyne has four stereogenic centers possessing a chlorine atom at C(7) and a *cis*-α,α'-disubstituted oxocene skeleton with a (*S*)-1-bromopropyl group at C(12) and a (*E*)-pent-2-en-4-ynyl group at C(6). The only total synthesis of (**6**) and (**7**) were reported by D. Kim and co-workers in 2003 based on the intramolecular amide enolate alkylation (IAEA).[12] (3*Z*)-Venustinene (**8**) containing a oxocene skeleton with a conjugated diene moiety and a propyl side chain was isolated from *Laurencia venusta* by E. Kurosawa in 1983.[13] In 2006, Laurendecumallene B (**9**) possessing a bromoallene moiety was isolated from *Laurencia nipponica* by V. A. Stonik.[14]

Figure 1. Representative Laurenan type of metabolites from *Laurencia* species



3. Previous Synthetic Approaches for Oxocene Natural Products

The investigation of synthetic approaches to construct the oxocene skeleton has been extensively documented since the first synthesis of (±)-Laurencin by T. Masamune in 1977.[15] In recent year, the synthetic community have reported the strategies for these halogenated metabolites considering various stereogenic centers and side chains, which impede the syntheses of diverse collections of oxocene natural product and their derivatives.

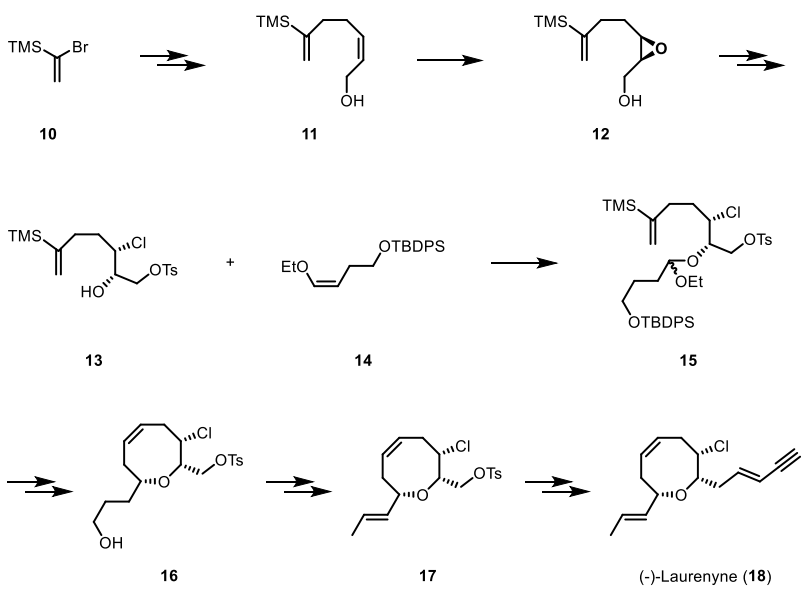
Although the development of efficient routes toward the oxocene natural products still investigate, the synthetic strategy to construct the eight-membered cyclic ether can be classified into three categories based on the methods reported to date.

3-1. Intramolecular Carbon-Carbon Bond Formation

In 1988, L. E. Overman and co-workers achieved the first total synthesis of (-)-Laurenyne (**18**) based on Prins cyclization to form the eight-membered cyclic ether and revised the absolute configuration for natural (+)-Laurenyne (**5**) to 2*R*, 7*R*, 8*R* (**Scheme 2**).[9] The synthesis began with the commercially available bromide **10,** which was converted to the alcohol

11 by the alkylation in the presence of BF_3·OEt, Still-Gennari olefination and the reduction with DIBAL-H. Asymmetric epoxidation of the alcohol **11** gave the epoxide **12** and the regioselective opening with triethylammonium chloride, followed by the selective tosylation of the resulting diol afforded the alcohol **13**. The substrate **15** for cyclization was obtained by the reaction of **13** with a slight excess of the enol ether **14,** which was prepared from ethoxyacetylene by the epoxide opening and the semihydrogenation. Prins cyclization of the acetal **15** in the presence of $SnCl_4$ followed by the desilylation gave the oxocene **16**, which was transformed into the tosylate **17** by PCC oxidation, Saegusa oxidation and the three-step of deoxygenation process. Cyanation of the tosylate **17** and subsequent reduction gave the aldehyde, and (-)-Laurenyne (**18**) was finally accomplished by Peterson reaction of the corresponding aldehyde followed by the removal of silyl group.

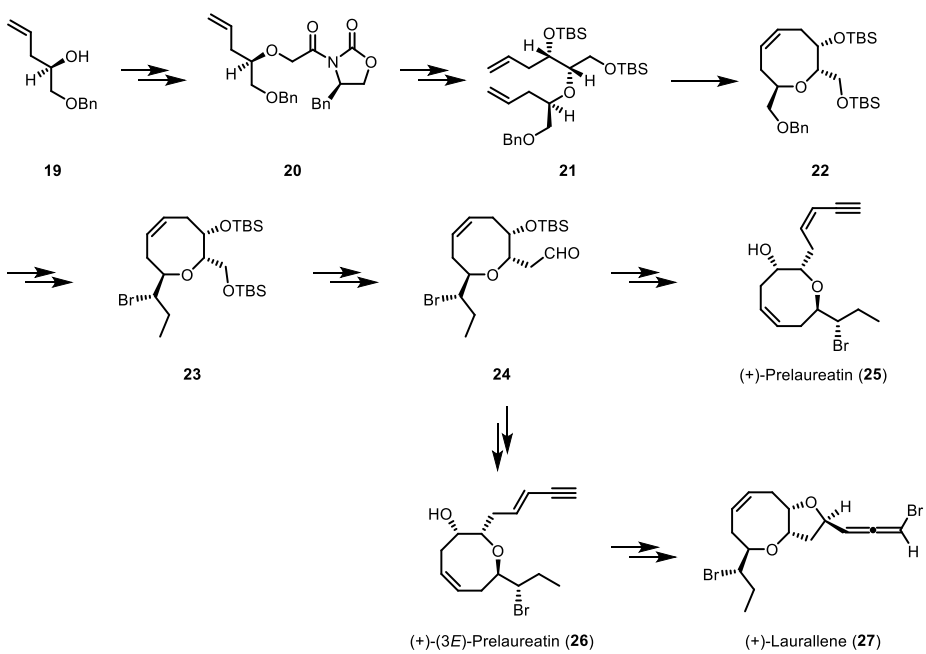
Scheme 2. Total synthesis of (-)-Laurenyne (**18**)



M. T. Crimmins and co-workers achieved the first total synthesis of (+)-Prelaureatin (**25**)

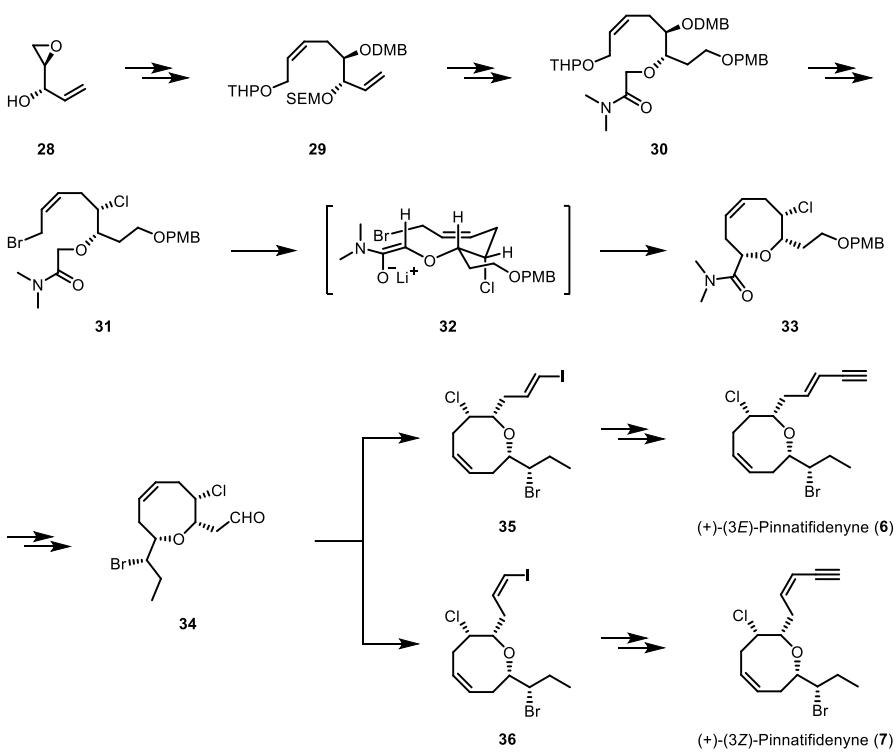
and (+)-Laurallene (**27**) based on the asymmetric aldol reaction and the ring-closing metathesis (RCM) in 2000 (**Scheme 3**).[16] The synthesis was started from the alcohol **19** which was transformed into the oxazolidinone **20** and the aldol reaction of **20** in the presence of $TiCl_4$, followed by the removal of the auxiliary gave the diol. TBS protection of the resulting diol afforded the diene **21**, which was converted to the oxocene **22** by RCM. Debenzylation, Swern oxidation and the addition of ethylmagnesium bromide could provide the secondary alcohol containing the propyl side chain of the natural products. Bromination of the resulting alcohol afforded the bromide **23,** which was converted to the aldehyde **24** by the four-step process including the selective desilylation, one-carbon extension and hydrolysis. (+)-Prelaureatin (**25**) was finally produced by the reaction of the aldehyde **24** using Stork's iodophosphorane, Sonogashira coupling with trimethylsilylacetylene and the desilylation.

Scheme 3. Total syntheses of (+)-Prelaureatin (**25**) and (+)-Laurallene (**27**)



(+)-Laurallene (**27**) was also synthesized *via* (+)-(3*E*)-Prelaureatin (**26**) which was obtained by Wittig reaction of the aldehyde **24**, followed by desilylation. Treatment of (**26**) with tetrabromocyclohexadienone (TBCO) according to the procedure by A. Murai finally produced (+)-Laurallene (**27**).

Scheme 4. Total syntheses of (+)-Pinnatifidenyne (**6**) and (**7**)



In 2003, D. Kim and co-workers accomplished the first total syntheses of (+)-(3*E*)- and (+)-(3*Z*)-Pinnatifidenyne ((**6**) and (**7**)) based on the intramolecular amide enolate alkylation (IAEA) (**Scheme 4**).[12] The syntheses began with the known optically active epoxide **28**, which was converted to the ether **29** by the regioselective epoxide opening under Yamaguchi conditions and the semihydrogenation using Lindlar catalyst. Regioselective hydro-

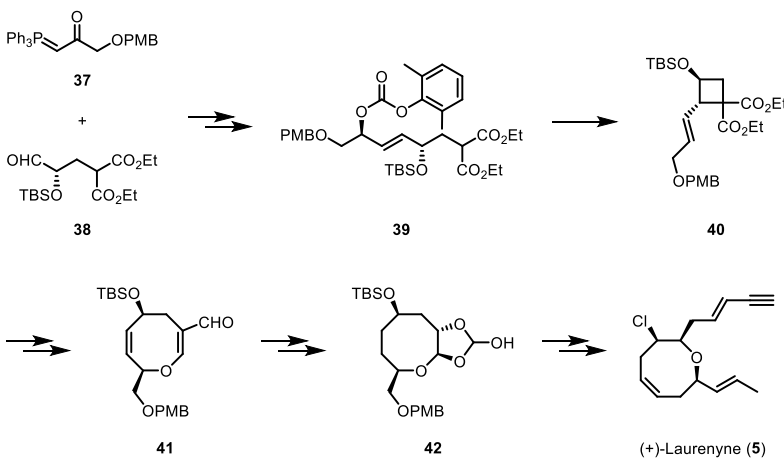
boration of the ether **29** and *O*-alkylation with 2-bromo-*N*,*N*-dimethylacetamide led to the amide **30**, which was transformed into the substrate **31** for cyclization by the chlorination and the bromination. Treatment of the substrate **31** with LiHMDS in THF provided the oxocene **33** *via* the rationalized transition state geometry **32** without a detectable amount of the corresponding S_N2' product. The bromopropyl side chain of the aldehyde **34** was installed by the seven-step of process including the direct ketone synthesis with ethylmagnesium bromide, the diastereoselective reduction, Mitsunobu reaction, the bromination and Dess-Martin oxidation. The aldehyde **34** was transformed into the (*E*)-vinyl iodide **35** by Takai olefination or the (*Z*)-vinyl iodide **36** by Stork olefination. Finally, Sonogashira coupling reaction of each (*E*)- and (*Z*)-vinyl iodide (**35** and **36**) and the removal of silyl group produced (+)-(3*E*)- and (+)-(3*Z*)-Pinnatifidenyne ((**6**) and (**7**)), respectively.

3-2. Intramolecular Carbon-Oxygen Bond Formation

R. K. Boeckman and co-workers achieved the total synthesis of (+)-Laurenyne (**5**) in 2002 (**Scheme 5**).[10] This group developed a synthetic method to construct the eight-membered cyclic ether using a retro-Claisen rearrangement. The synthesis began with the condensation of the known ylide **37** and aldehyde **38**, which was prepared from the optically active diol. The resulting enone was converted to the substrate **39** for the S_N2' cyclization by Corey-Bakshi-Shibata (CBS) reduction and esterification. Treatment of the allylic carbonate **39** with NaH in refluxing toluene produced the cyclobutane **40** as a single diastereomer. Reduction of the diester **40**, followed by Dess-Martin oxidation and subsequent thermal equilibration *via* the key retro-Claisen rearrangement could construct the eight-membered cyclic ether **41**. The aldehyde **41** was selectively reduced and decarbonylated to give the oxocene, which was transformed into the hemiacetal **39** by the epoxidation and the directly opening with the lithium enolate of acetaldehyde *N*,*N*-dimethyl hydrazone. (+)-Laurenyne

(**5**) was finally achieved through the enyne formation by Wittig reaction, CBS reduction, followed by the chlorination of the resulting alcohol.

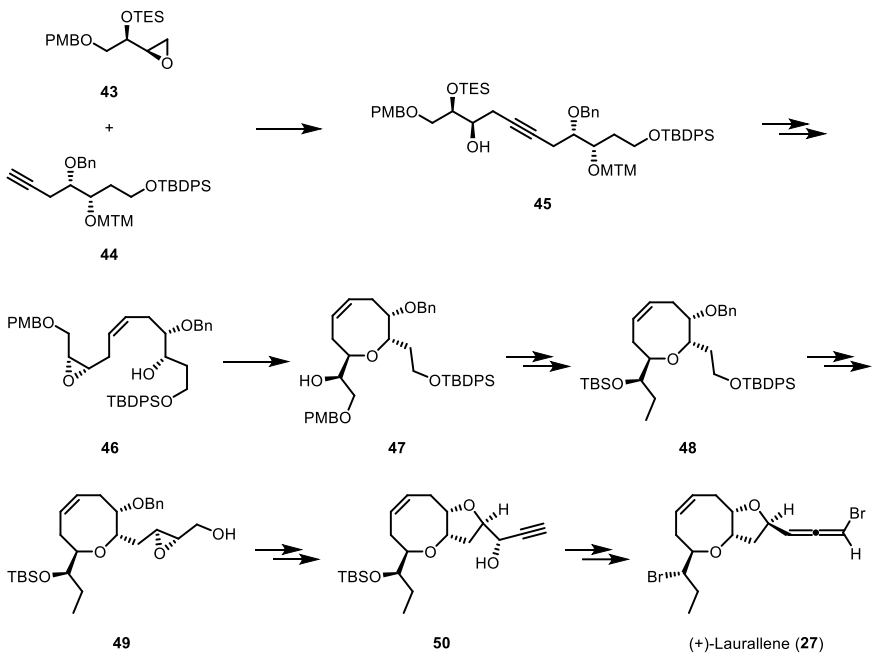
Scheme 5. Total synthesis of (+)-Laurenyne (**5**)



In 2003, T. Suzuki and co-workers accomplished the total synthesis of (+)-Laurallene (**27**) base on the *exo*-cyclization of hydroxyl *cis*-epoxide promoted by $Eu(fod)_3$ (**Scheme 6**).[17] The synthesis was started from the coupling of epoxide **43** and acetylene **44**, which were prepared from (-)-diethyl D-tartrate and D-(+)-ribonic γ-lactone, by the Yamaguchi method to afford the alcohol **45**. Mesylation and cleavage TES ether of the corresponding alcohol **45**, followed by the treatment with the base provided the epoxide, which was converted to the substrate **46** for cyclization by the partial hydrogenation. The substrate **46** was cyclized with $Eu(fod)_3$ in refluxing toluene to afford the oxocene **47**, which was transformed into the ether **48** by the seven-step process including the epoxide formation and the regioselective methylation with Me_2CuLi to install the propyl side chain. After the removal of TBDPS group, Dess-Martin oxidation of the resulting alcohol followed by Horner-Wadsworth-Emmons olefination provided the alcohol, which was converted to the epoxide **49** by Sharpless

epoxidation. The propargyl alcohol **50** was derived from the epoxide **49** *via* the protection/ deprotection sequence and the Corey method. The bromoallene formation according to the Overman method and the bromination finally produced (+)-Laurallene (**27**).

Scheme 6. Total synthesis of (+)-Laurallene (**27**)

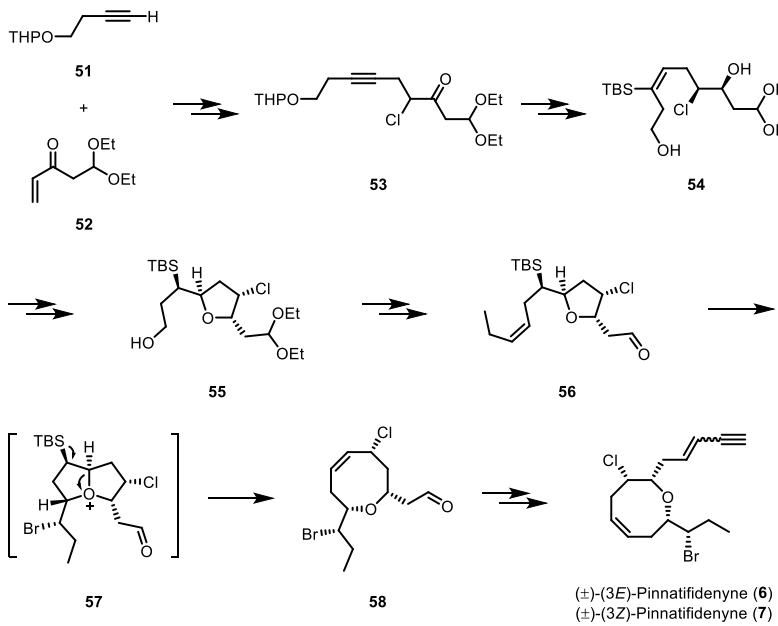


3-3. Ring Expansion

S. A. Snyder and co-workers achieved the racemic formal synthesis of (±)-Pinnatifidenyne ((**6**) and (**7**)) based on the diastereoselective ring-expanding bromoetherification of tetra-hydrofuran (**Scheme 7**).[18] The synthesis began with the addition of the alkyne **51** into the enone **52** in Michael-type fashion in the presence of TBSOTf. The resulting silyl enol ether was exposed to TBAF with NCS to afford the α-chloroketone **53**, which was transformed into the diol **54** by the three-step process including the homopropargyl alcohol protection with dimethylvinylsilyl (DMVS) group, the hydrosilylation using TBSH in the presence of

Karstedt's catalyst and the removal of DMVS group. The bromonium-induced cyclization with NBS and Ph_3PS, followed by radical reduction provided the alcohol **55**, which was converted to the substrate **56** by the sequence of Swern oxidation and the one-pot Wittig olefination/acetal cleavage process. Treatment of the substrate **56** with the unique bromonium source (BDSB, $Et_2SBr{\cdot}SbBrCl_5$) generated the aldehyde **57**, which was previously reported by D. Kim and co-workers in 2003 through the oxonium intermediate **58**, and the racemic formal synthesis of (±)-Pinnatifidenyne ((**6**) and (**7**)) was finally accomplished.

Scheme 7. Racemic formal synthesis of (±)-Pinnatifidenyne (**6**) and (**7**)



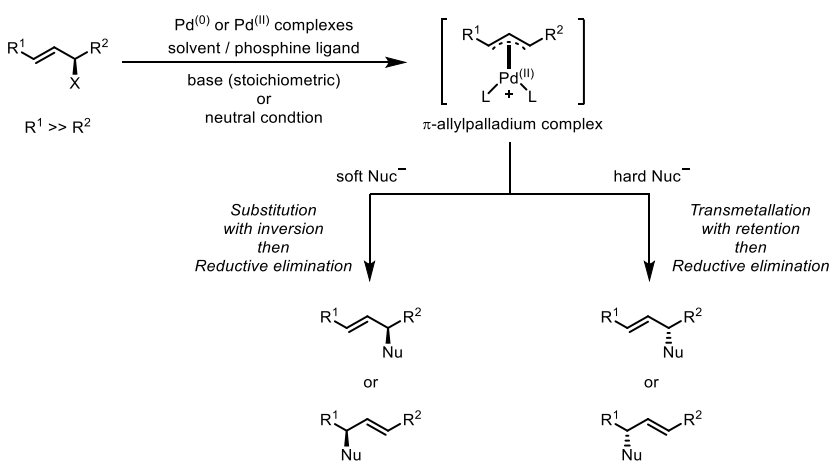
Although various interesting synthetic routes to construct the oxocene skeleton of the marine natural products from *Laurencia* species have been reported to date, there still are remained requirements for the generally unified strategy. With this synthetic attention in mind, we have developed the new synthetic strategy for the oxocene skeleton.

4. Pd(0)-Catalyzed Cyclization

4-1. Tsuji-Trost Allylic Alkylation

Transition metals, having a special potential to activate diverse organic compounds, have led to the development of various catalytic organic reactions. In particular, asymmetric metal-catalyzed reactions using palladium have a wide range of applications in organic chemistry. Since the initial report by J. Tsuji and co-workers in 1965, B. M. Trost and co-workers reported the work using alkyl-substituted π-allylpalladium complexes with the complete regio- and stereoselectivity in 1973 and this transformation is generally called Tsuji-Trost reaction (**Scheme 8**).[19] The asymmetric allylic alkylation using palladium can form diverse type of bonds including C-C, C-N and C-O bond. Above all, palladium catalyzed cyclization has been considered as one of the most powerful synthetic tool to construct the complex carbo- or heterocycles in natural products.

Scheme 8. Tsuji-Trost allylic alkylation



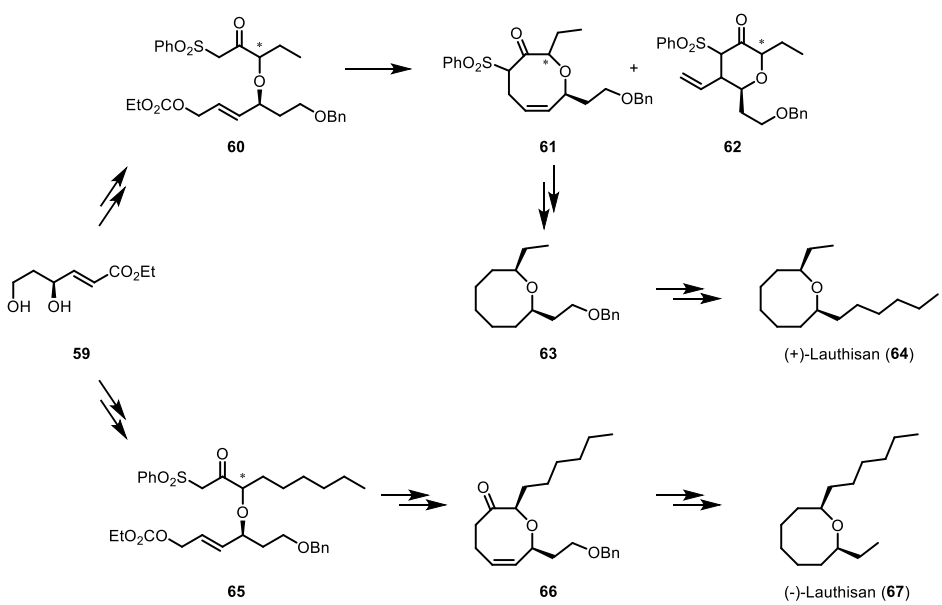
The oxidative addition of palladium to allylic substrates, such as acetates, carbonates, halides and carbamates, produced π-allylpalladium complex. The regioselectivity generally

determined by steric factors, favoring attack to the less hindered position, but can be influenced by the property of ligands or nucleophiles. The formation of π-allylpalladium complex contains inversion of stereochemistry by oxidative addition of palladium catalyst, and the soft nucleophile substitutes with inversion. Thus, the product can be obtained with an overall retention of configuration (double inversion). On the other hand, the hard nucleophile attack with retention by transmetallation then the optically active substrate can be obtained with an overall inversion of configuration.

4-2. Previous Synthetic Applications to Oxocane Skeleton

In our group, the efficient synthetic route for the construction of eight-membered cyclic ether *via* the intramolecular Tsuji-Trost allylic alkylation was developed. As its application, we reported the syntheses of (+)-Lauthisan (**64**) and (-)-Lauthisan (**67**), the primary target of synthetic studies for oxocane skeleton, in 1995 (**Scheme 9**).[20]

Scheme 9. Total syntheses of (+)-Lauthisan (**64**) and (-)-Lauthisan (**67**)



Our synthetic strategy involves a direct construction of oxocane skeleton, the eight-membered cyclic ether, by unusually regioselective Pd(0)-catalyzed cyclization of acyclic allylic carbonate **60**. The cyclization precursor **60** was derived from the optically active ester **59** by *O*-alkylation, esterification and allylic carbonate formation as key features. The eight-membered cyclic ether **61** was obtained as the major isomer with 6.8:1 ratio, along with the six-membered cyclic ether **62** *via* Pd(0)-catalyzed allylic alkylation and the *cis*-isomer **63** was afforded by the careful desulfonylation and subsequent base promoted equilibration. Finally, the synthesis of (+)-Lauthisan (**64**) was accomplished by the sequential of reduction and deoxygenation and (-)-Lauthisan (**67**) was obtained under the similar synthetic routes.

Based on these results, our group decided to apply this synthetic strategy to more complicated marine natural products containing oxocene skeleton from *Laurencia* species.

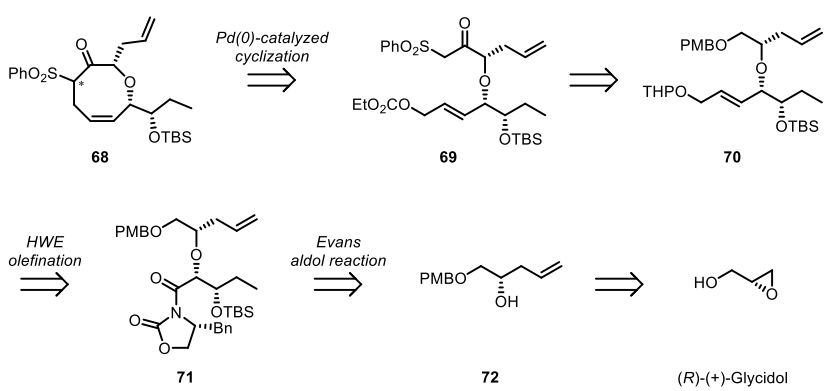
II. Results and Discussion

1. Asymmetric Total Synthesis of (+)-(3*E*)-Pinnatifidenyne (6)

1-1. Synthetic Strategy for Pd(0)-Catalyzed Cyclization

Our group reported the total syntheses of (+) and (-)-Lauthisan ((**64**) and (**67**)) *via* Pd(0)-catalyzed cyclization and we expected this synthetic strategy to use for various oxocene natural products. Encouraged by this route, we undertook the total synthesis of (+)-(3*E*)-Pinnatifidenyne (**6**) and other oxocene natural products.

Scheme 10. Retrosynthetic analysis of Pd(0)-catalyzed cyclization

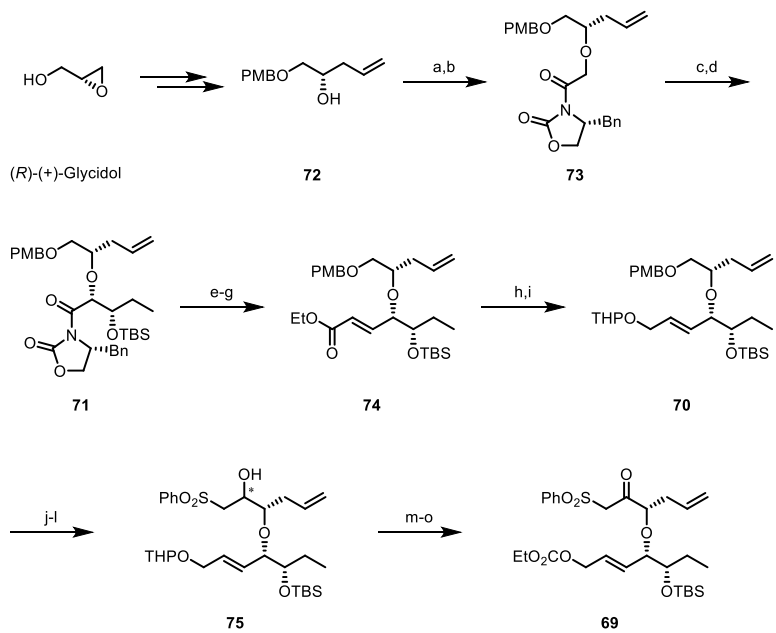


Our synthetic plan is outlined in **Scheme 10**, focusing on the construction of oxocene skeleton *via* Pd(0)-catalyzed cyclization with the properly functionalized precursor **69**. The cyclization precursor **69** could be obtained from ether **70**, which was prepared from the aldol adduct **71** *via* Horner-Wadsworth-Emmons olefination, by the alkylation with methyl phenyl sulfone and allylic carbonate formation. The aldol adduct **71**, which was containing a *cis*-orientation at the α- and α'-position to the ether linkage, was derived from the known

alcohol **72** through the aldol reaction using Evans auxiliary. The known alcohol **72** was conveniently prepared from the commercially available (*R*)-(+)-Glycidol by the simple modifications.[21]

1-2. Preparation of Pd(0)-Catalyzed Cyclization Precursor 69

Scheme 11. Preparation of Pd(0)-catalyzed cyclization precursor **69**



Reagents and conditions: (a) iodoacetic acid, NaH, THF, 0 °C to 50 °C; (b) PivCl, TEA, *n*-BuLi, (*R*)-4-benzyl-2-oxazolidinone, THF, -78 °C, 93% for 2 steps; (c) propionaldehyde, *n*-Bu_2BOTf, TEA, CH_2Cl_2, -78 °C to 0 °C, 72%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95%; (e) $LiBH_4$, MeOH, Et_2O, 0 °C, 88%; (f) TPAP, NMO, 4Å MS, CH_2Cl_2, 0 °C; (g) triethyl phosphonoacetate, *t*-BuOK, THF, 0 °C, 64% for 2 steps; (h) DIBAL-H, CH_2Cl_2, 0 °C, 83%; (i) DHP, PPTS, CH_2Cl_2, 0 °C, 100%; (j) DDQ, CH_2Cl_2/pH 7 buffer solution (10:1), rt, 61%, (k) TPAP, NMO, 4Å MS, CH_2Cl_2, 0 °C; (l) methyl phenyl sulfone, *n*-BuLi, THF, -78 °C, 80% for 2 steps; (m) DMP, $NaHCO_3$, CH_2Cl_2, rt, 88%; (n) PPTS, EtOH, THF, 0 °C, 84%; (o) ethylchloroformate, pyridine, CH_2Cl_2, 0 °C, 88%

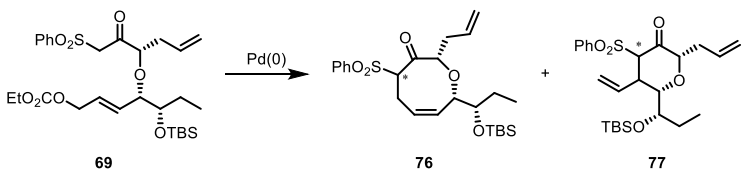
The synthesis commenced with the preparation of precursor **69** for Pd(0)-catalyzed cyclization, as shown in **Scheme 11**. Esterification of the alcohol **72**, which was prepared from commercially available (*R*)-(+)-Glycidol, with sodium salt of iodoacetic acid afforded the acid intermediate. The acid intermediate was activated by pivaloyl chloride, the resulting mixed anhydride was converted to the oxazolidinone **73** by the addition of the lithiated Evans auxiliary. Aldol reaction of **73** in the presence of *n*-Bu_2BOTf and propionaldehyde provided the *syn*-alcohol and subsequent TBS protection afforded the aldol adduct **71**.[22] Reductive removal of the auxiliary of **71** followed by the sequential oxidation and Horner-Wadsworth-Emmons olefination produced the ester **74**.[23] Reduction of the ester **74** and the protection of the corresponding alcohol with THP afforded the ether **70**. Deprotection of PMB group of the ether **70**, followed by the oxidation of the resulting alcohol and the alkylation with the anion of methyl phenyl sulfone gave the secondary alcohol **75**. Transformation of the secondary alcohol **75** into the precursor **69** was achieved by the oxidation of the alcohol **75** followed by THP deprotection of the resulting ketone, and then allylic carbonate formation.

1-3. Synthetic Studies for Oxocene 76

With the precursor **69** in hand, we intensively investigated the regioselective Pd(0)-catalyzed cyclization as summarized in **Table 2**. After the optimization under the various reaction conditions including ligands, solvent and temperature, it was determined that the intramolecular allylic alkylation of **69** in the presence of $Pd(dppe)_2$ in DMSO at 70 ℃ afforded the oxocene **76** in a 76% isolated yield with the best regioselectivity (9.5:1, Entry 7).[24] The reaction did not proceed in THF at the temperature below 60 ℃ (Entry 1) and the conversion of cyclization could be better at 70 ℃ (Entry 2). Among various solvents, DMSO gave the better selectivity than THF (Entry 7, Entry 2) and MeCN provided the inverse

selectivity (Entry 3). Interestingly, the cyclization with other ligands such as dppm, dppb or dppf only produced the six-membered cyclic ether **77** (Entry 8-10).

Table 2. Pd(0)-catalyzed cyclization of allylic carbonate **69**



69 **76** **77**

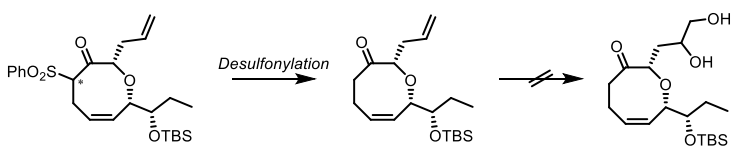
Entry	Catalyst (3mol%)	Solvent	Temperature	Ratio (**76** : **77**)
1		THF	rt to 60 ℃	NR
2			**70 ℃**	4 : 1
3		MeCN		1 : 1.4
4	**$Pd(dppe)_2$**	Acetone		1.5 : 1
5		Toluene		1.8 : 1
6		$CHCl_3$		Decomposed
7		**DMSO**		**9.5 : 1**
8	$Pd_2(dppm)_3$			0 : 1
9	$Pd(dppb)_2$			0 : 1
10	$Pd(dppf)_2$			0 : 1
11	$Pd(PPh_3)_4$			NR

The removal of the sulfone group was needed to confirm the exact structure and proceed to the natural product, because the oxocene **76** is the mixture of two inseparable diastereomers (**Table 3**). Desulfonylation of **76** by Birch condition using Na and liquid NH_3 in THF provided the desired oxocene **78** as we expected (Entry 5), however, the general condition using 5% Na/Hg in the presence of the various buffers such as Na_2HPO_4, AcOH or $B(OH)_3$

could not produce the product (Entry 1-4).[25]

Next, we envisioned the selective dihydroxylation of the terminal olefin in **78** before the isomerization of the inside double bond to the proper position, disappointingly, the diol **79** was not afforded.

Table 3. Desulfonylation of oxocene **76**

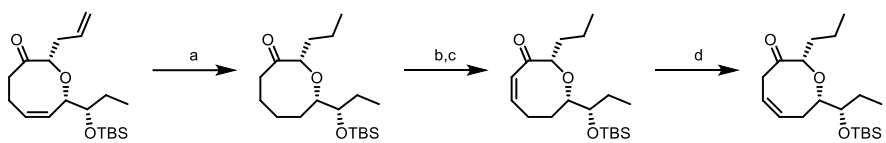


76 **78** **79**

Entry	Reaction conditions	Result
1	5% Na/Hg, Na_2HPO_4, MeOH, -78 to -40 ℃	NR
2	5% Na/Hg, AcOH, MeOH, -78 to -40 ℃	NR
3	5% Na/Hg, AcOH, MeOH, -20 ℃	Decomposed
4	5% Na/Hg, $B(OH)_3$, MeOH, rt	Trace
5	Na/NH_3, THF, -78 ℃	71%

Although we could not obtain the desired result to selectively cleave the terminal olefin, we were having the model study to afford the ketone **82** which was containing the inside olefin at the same position as the natural product (**Scheme 12**). Hydrogenation of **78** with 10 wt% Pd/C under the hydrogen atmosphere afforded the oxocane **80** which was converted to the α,β-unsaturated ketone **81** by Saegusa oxidation involving the formation of silyl enol ether followed by the treatment with $Pd(OAc)_2$.[26] To our delight, deconjugated isomerization with DBU of the resulting α,β-unsaturated ketone **81** successfully afforded the desired ketone **82** with a 80% isolated yield.[27]

Scheme 12. Model study for deconjugative isomerization



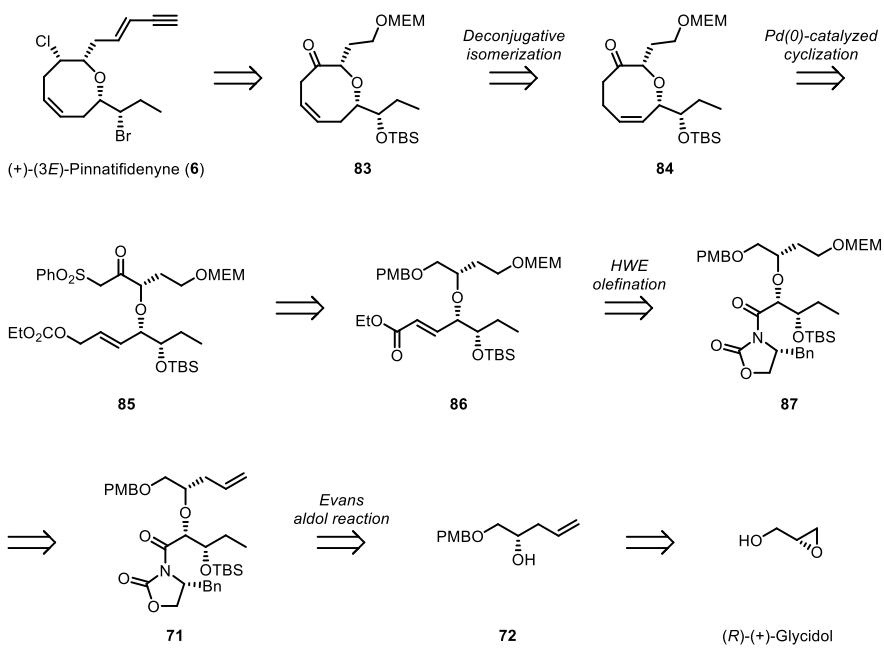
Reagents and conditions: (a) 10 wt% Pd/C, H_2, EtOAc/MeOH (3:1), rt, 100%; (b) TMSOTf, TEA, CH_2Cl_2, -78 °C; (c) $Pd(OAc)_2$, MeCN, rt, 95% for 2 steps; (d) DBU, CH_2Cl_2, rt, 80%

Based on these results, we recognized that the precursor **69** was not suitable though Pd(0)-catalyzed cyclization is still useful tool to construct the oxocene skeleton, and the redesign of the precursor for the regioselective cyclization was needed to approach the oxocene natural products.

1-4. Retrosynthetic Analysis of (+)-(3*E*)-Pinnatifidenyne (6)

As we mentioned above, the precursor **69** was needed the redesign to proceed (+)-(3*E*)-Pinnatifidenyne (**6**) because the regioselective dihydroxylation of the terminal olefin in **78** could not provide the diol **79**. Our retrosynthetic analysis is outlined in **Scheme 13**. The halides including chloride at C(7) and bromide at C(13) and the enyne moiety would be introduced at the final stage with the ketone **83**. The ketone **83** would be obtained from the oxocene **84** by the deconjugative isomerization as we tested with the α,β-unsaturated ketone **81** and the oxocene **84** would be provided by Pd(0)-catalyzed cyclization with the rede-signed precursor **85**, which could be transformed from the ether **87** by Horner-Wadsworth-Emmons olefination and the alkylation of methyl phenyl sulfone. The ether **87** would be obtained from the aldol adduct **71** by the sequence of the dihydroxylation of the terminal olefin, oxidative cleavage followed by the subsequent reduction of the resulting aldehyde.

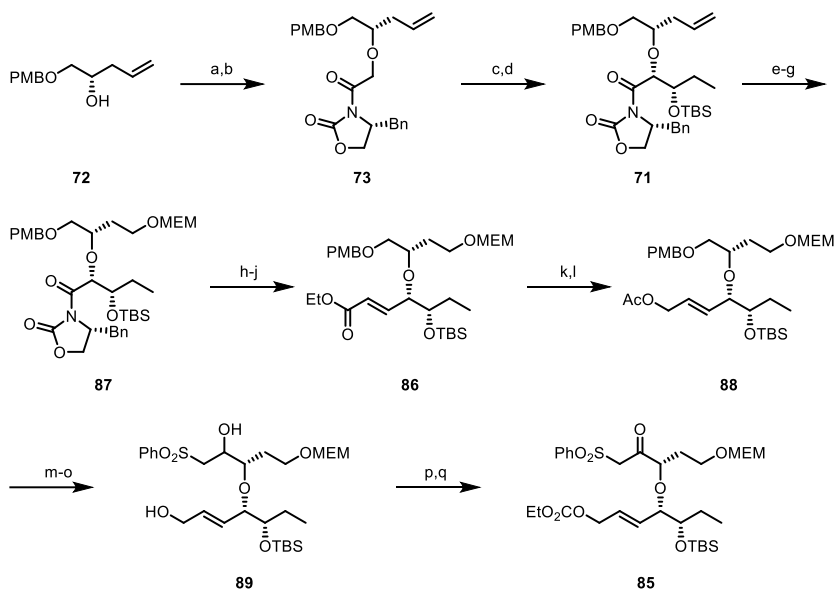
Scheme 13. Retrosynthetic analysis of (+)-(3*E*)-Pinnatifidenyne (**6**)



1-5. Preparation of Pd(0)-Catalyzed Cyclization Precursor 85

Dihydroxylation of the aldol adduct **71**, which was prepared from the known alcohol **72**, followed by the subsequent oxidative cleavage gave the aldehyde, which was converted to the ether **87** by the reduction of the corresponding aldehyde and MEM protection. Removal of the chiral auxiliary of the ether **87**, followed by the oxidation of the resulting alcohol and Horner-Wadsworth-Emmons olefination provided the ester **86**. Reduction of the ester **86** with DIBAL-H and the acetylation of the corresponding alcohol gave the ether **88**, which was transformed into the diol **89** by the deprotection of PMB group with DDQ, the oxidation of the resulting alcohol and the alkylation with the anion of methyl phenyl sulfone. The precursor **85** for the intramolecular allylic alkylation was achieved by the selective carbonate formation of the primary alcohol of the diol **89** and Dess-Martin oxidation of the remaining secondary alcohol (**Scheme 14**).

Scheme 14. Preparation of Pd(0)-catalyzed cyclization precursor **85**



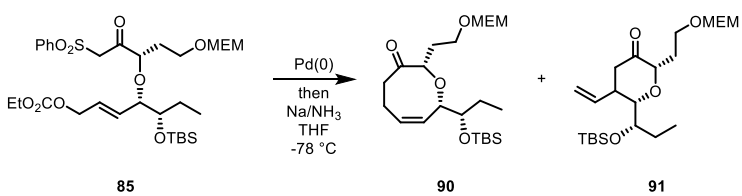
Reagents and conditions: (a) iodoacetic acid, NaH, THF, 0 °C to 50 °C; (b) PivCl, TEA, *n*-BuLi, (*R*)-4-benzyl-2-oxazolidinone, THF, -78 °C, 93% for 2 steps; (c) propionaldehyde, *n*-Bu_2BOTf, TEA, CH_2Cl_2, -78 °C to 0 °C, 72%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95%; (e) OsO_4, NMO, *t*-BuOH /THF/H_2O (5:5:1), rt then $NaIO_4$, 0 °C; (f) BH_3·THF, THF, 0 °C, 79% for 2 steps; (g) MEMCl, DIPEA, K_2CO_3, CH_2Cl_2, 0 °C, 96%; (h) $LiBH_4$, MeOH, Et_2O, 0 °C, 97%; (i) DMP, $NaHCO_3$, CH_2Cl_2, rt; (j) triethyl phosphonoacetate, *t*-BuOK, THF, 0 °C, 96% for 2 steps; (k) DIBAL-H, CH_2Cl_2, 0 °C, 85%; (l) Ac_2O, TEA, DMAP, CH_2Cl_2, 0 °C, 97%; (m) DDQ, CH_2Cl_2/pH 7 buffer solution (10:1), rt, 96%, (n) TPAP, NMO, 4Å MS, CH_2Cl_2, 0 °C; (o) methyl phenyl sulfone, *n*-BuLi, THF, -78 °C, 70% for 2 steps; (p) ethylchloroformate, pyridine, CH_2Cl_2, 0 °C, 81%; (q) DMP, $NaHCO_3$, CH_2Cl_2, rt, 100%

1-6. Pd(0)-Catalyzed Cyclization of Allylic Carbonate 85

With the precursor **85** in hand, we investigated the regioselective Pd(0)-catalyzed cyclization under the various reaction conditions including ligands, solvent and temperature as summarized in **Table 4**. The ratio of the desired oxocene **90** to the tetrahydropyran **91** was determined by the subsequent desulfonylation by Birch condition because two regioisomers

were not separable by the flash column chromatography unlike the cyclization with the precursor **69**. To our delight, the intramolecular allylic alkylation of **85** in the presence of $Pd(dppe)_2$ in THF at 45 ℃ afforded the oxocene **90** in an 87% isolated yield with the best regioselectivity (23.8:1, Entry 6). Interestingly, the reaction temperature was decreased to 45 ℃ and the regioselectivity was quite improved with the redesigned precursor **85**. Among the various solvents, THF gave the better selectivity than DMSO (Entry 6, Entry 2) and Toluene did not proceed the reaction (Entry 4). The cyclization with other ligands such as dppm, dppb, dppf or PPh_3 afforded only the tetrahydropyran **91** with the moderate yield or the recovered precursor **85** (Entry 7-10).

Table 4. Pd(0)-catalyzed cyclization of allylic carbonate **85**



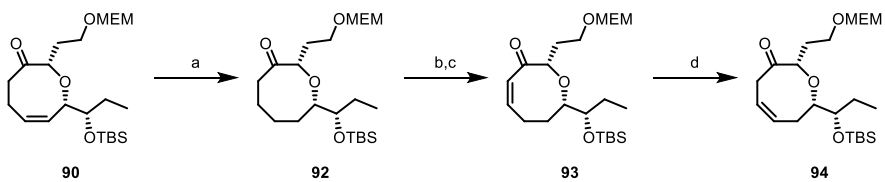
85 **90** **91**

Entry	Catalyst (3mol%)	Solvent	Temperature	Ratio (**90** : **91**)
1	**$Pd(dppe)_2$**	DMSO	rt to 35 ℃	NR
2			**45 ℃**	4 : 1
3		MeCN		1 : 3.2
4		Toluene		NR
5		$CHCl_3$		Decomposed
6		**THF**		**23.8 : 1**
7	$Pd_2(dppm)_3$			NR
8	$Pd(dppb)_2$			0 : 1
9	$Pd(dppf)_2$			0 : 1
10	$Pd(PPh_3)_4$			NR

1-7. Approaches to Diastereoselective Reduction of Ketone 94

After the preparation of the oxocene **90**, we executed the sequential process of the deconjugative isomerization for the ketone **94** as shown in **Scheme 15**. We first transformed the oxocene **90** into the oxocane **92** by the hydrogenation using 10 wt% Pd/C under the hydrogen atmosphere and Saegusa oxidation of the oxocane **92**, followed by the deconjugative isomerization with DBU afforded the ketone **94** having the inside double bond at the proper position.

Scheme 15. Olefin isomerization of the oxocene **90**



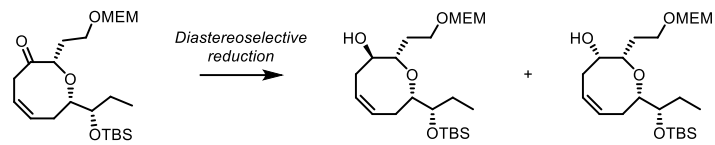
Reagents and conditions: (a) 10 wt% Pd/C, H_2, EtOAc/MeOH (3:1), rt, 90%; (b) LiHMDS, TMSCl, TEA, THF, -78 ^oC; (c) $Pd(OAc)_2$, MeCN, rt, 78% for 2 steps; (d) DBU, CH_2Cl_2, rt, 87%

For the completion of the synthesis of (+)-(3*E*)-Pinnatifidenyne (**6**), the diastereoselective reduction of the ketone **94** was significant process to obtain the desired *anti* alcohol **95** which was converted to the chloride functionality at C(7).

With the ketone **94** in hand, we performed the intensive optimization of the diastereoselective reduction under the various reaction conditions as summarized in **Table 5**. Among the various reaction conditions, the reduction of the ketone **94** using DIBAL-H in Toluene afforded the inseparable mixture of two diastereomer as the desired *anti* alcohol **95** and the *syn* alcohol **96**, in a 89% yield with the best diastereoselectivity (1.9 : 1, Entry 4), and the desired *anti* alcohol **95** could be identified with the result of CBS reduction (Entry 10).[28]

Interestingly, reduction with $NaBH_4$ or LAH gave the *syn* alcohol **96**, which was converted to the desired *anti* alcohol **95** by Mitsunobu inversion, as major product with the inverse diastereoselectivity (Entry 7, Entry 9).

Table 5. Diastereoselective reduction of ketone **94**



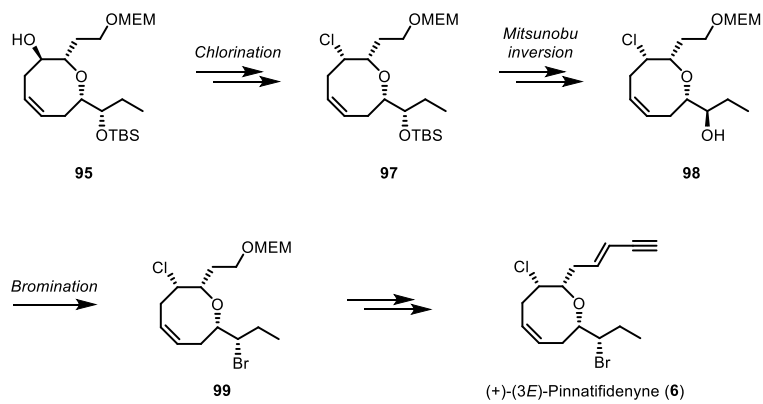
94 **95** **96**

Entry	Reaction conditions	Ratio (**95** : **96**)
1	L-selectride, THF, -78 ℃	1.7 : 1
2	K-selectride, THF, -78 ℃	1.7 : 1
3	Superhydride, THF, -78 ℃	1.1 : 1
4	**DIBAL-H, Toluene, -78 ℃**	**1.9 : 1**
5	Red-Al, , THF, -78 ℃	1 : 1.1
6	LiAl(*t*-BuO)$_3$H, , THF, -78 ℃	1 : 1.5
7	$NaBH_4$, MeOH, -78 ℃	1 : 3.3
8	$NaBH_4$, $CeCl_3$, MeOH, -78 ℃	1 : 1.5
9	LAH, THF, -78 ℃	1 : 5
10	(*R*)-(+)-*α*,*α*-diphenyl-2-pyrrolidinemethanol catecholborane, Toluene, -20 ℃	1.5 : 1

Unfortunately, we could not obtain the satisfactory result because of some reasons. As we mentioned above, the two diastereomeric mixture were not separable and the installation of the ring chlorine functionality at C(7) as the next step was crucial for the completion of our synthesis because it was well-known that the undesired elimination of the secondary hydroxyl group in **95** and **96** gave the diene compound as the byproduct under the standard

reaction condition of the chlorination. Moreover, Mitsunobu inversion of the hydroxyl group at C(13) to afford the epimeric alcohol **98** was surely needed to be transformed into the oxocene **99** by the bromination, however this would be the synthetic hurdle in the cyclic haloether system (**Scheme 16**). Based on these results, we finally suggested the further modified precursor to revise the impeding factors for the total synthesis of (+)-(3*E*)-Pinnatifidenyne (**6**).

Scheme 16. Approaches to (+)-(3*E*)-Pinnatifidenyne (**6**)

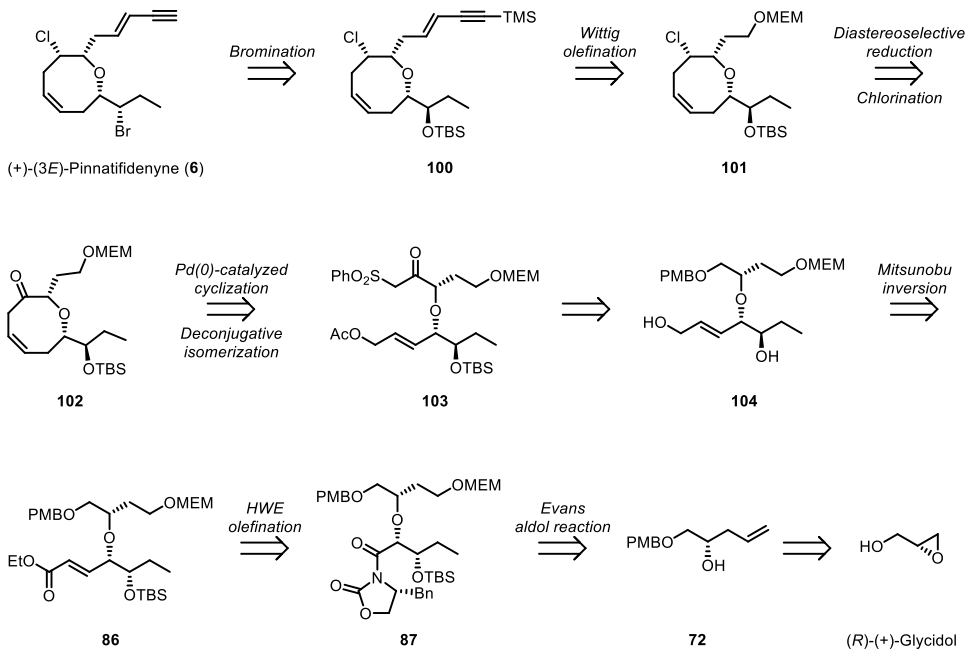


1-8. Revised Retrosynthetic Analysis of (+)-(3*E*)-Pinnatifidenyne (6)

Our revised retrosynthetic approach for (+)-(3*E*)-Pinnatifidenyne (**6**) is shown in **Scheme 17**, which includes the newly designed precursor **103** containing the epimeric hydroxyl group at C(13) for the bromide functionality in our target natural product (**6**). This bromide would be introduced *via* the global deprotection of silyl groups, followed by the standard Appel reaction of the (*E*)-enyne **100** with CBr_4 at the final stage and the (*E*)-enyne moiety would be constructed by the Wittig olefination. The labile ring chlorine functionality at C(7) could be installed through the sequential process of the diastereoselective reduction and the modified chlorination of the oxocene **102**, which would be effectively prepared *via*

deconjugative isomerization and the regioselective Pd(0)-catalyzed cyclization of the newly designed precursor **103**. This allylic acetate **103** could be prepared from the diol **104** which would be obtained from the ester **86** by Mitsunobu inversion of the hydroxyl group at C(13) as the key modification. The ester **86** would be afforded by Horner-Wadsworth-Emmons olefination of the aldol adduct **87**, containing the *cis*-α,α'-substituted ether linkage, which would be expected to be conveniently prepared from the commercially available (*R*)-(+)-Glycidol.

Scheme 17. Revised retrosynthetic analysis of (+)-(3*E*)-Pinnatifidenyne (**6**)

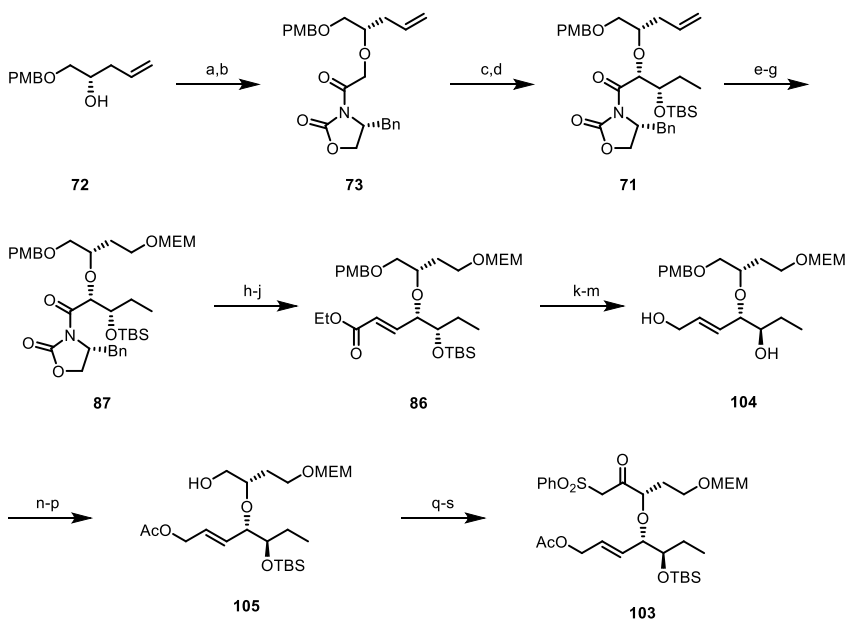


1-9. Preparation of Pd(0)-Catalyzed Cyclization Precursor 103

The total synthesis of (+)-(3*E*)-Pinnatifidenyne (**6**) was commenced with the preparation of the cyclization precursor **103** as shown in **Scheme 18**. Etherification of the known alcohol **72** with sodium salt of iodoacetic acid provided the acid intermediate, which was con-

verted to the oxazolidinone **73** through the activation with pivaloyl chloride, followed by the addition of lithiated Evans auxiliary to the corresponding mixed anhydride. Aldol reaction of **73** with propionaldehyde in the presence of *n*-Bu_2BOTf provided the *syn*-alcohol and subsequent TBS protection afforded the aldol adduct **71**.

Scheme 18. Preparation of Pd(0)-catalyzed cyclization precursor **103**



Reagents and conditions: (a) iodoacetic acid, NaH, THF, 0 °C to 50 °C; (b) PivCl, TEA, *n*-BuLi, (*R*)-4-benzyl-2-oxazolidinone, THF, -78 °C, 93% for 2 steps; (c) propionaldehyde, *n*-Bu_2BOTf, TEA, CH_2Cl_2, -78 °C to 0 °C, 72%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95%; (e) OsO_4, NMO, *t*-BuOH /THF/H_2O (5:5:1), rt then $NaIO_4$, 0 °C; (f) BH_3·THF, THF, 0 °C, 79% for 2 steps; (g) MEMCl, DIPEA, K_2CO_3, CH_2Cl_2, 0 °C, 96%; (h) $LiBH_4$, MeOH, Et_2O, 0 °C, 97%; (i) DMP, $NaHCO_3$, CH_2Cl_2, rt; (j) triethyl phosphonoacetate, *t*-BuOK, THF, 0 °C, 96% for 2 steps; (k) TBAF, THF, rt, 100%; (l) DEAD, PPh_3, *p*-nitrobenzoic acid, THF, rt; (m) LAH, THF, 0 °C, 78% for 2 steps; (n) Ac_2O, TEA, DMAP, CH_2Cl_2, -10 °C, 98%; (o) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 100%; (p) DDQ, CH_2Cl_2/pH 7 buffer solution (10:1), rt, 95%, (q) DMP, $NaHCO_3$, CH_2Cl_2, rt; (r) methyl phenyl sulfone, *n*-BuLi, THF, -78 °C, 72% for 2 steps; (s) DMP, $NaHCO_3$, CH_2Cl_2, rt, 100%

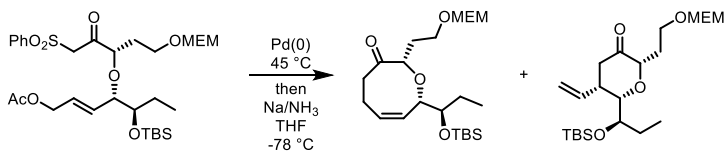
Dihydroxylation of the terminal olefin of the aldol adduct **71** and spontaneous oxidative cleavage afforded the aldehyde, which was transformed into the ether **87** by the reduction of the resulting aldehyde and MEM protection. Reductive removal of the chiral auxiliary of **87** with $LiBH_4$, followed by the sequential oxidation of the corresponding alcohol and Horner-Wadsworth-Emmons olefination provided the ester **86**. TBS deprotection of the ester **86** and Mitsunobu inversion of the resulting secondary hydroxyl group, followed by the subsequent treatment with LAH afforded the diol **104** including the desired stereochemistry of the hydroxyl group at C(13) for the bromination at the final stage of our synthesis.[29] Chemoselective acetylation to the primary hydroxyl group of the diol **104** and TBS protection of the remaining hydroxyl group, followed by PMB deprotection with DDQ gave the alcohol **105**. Oxidation of the alcohol **105** and the alkylation with the anion of methyl phenyl sulfone into the corresponding aldehyde provided smoothly the secondary alcohol without deacetylation. The allylic acetate **103** as the precursor for our key strategy was successfully achieved *via* Dess-Martin oxidation.

1-10. Pd(0)-Catalyzed Cyclization of Allylic Acetate 103

With the precursor **103** in hand, we intensively performed the regioselective Pd(0)-catalyzed cyclization under the various reaction conditions including ligands and solvents as summarized in **Table 6**. The desired oxocene **106** and the tetrahydropyran **107** were determined by the subsequent desulfonylation by Birch condition because the regioisomeric mixtures which were obtained from the cyclization were inseparable by the flash column chromatography. To our delight, Pd(0)-catalyzed cyclization of allylic acetate **103** using the combination of $Pd(dppe)_2$ and MeCN afforded the desired oxocene **106** in a 92% isolated yield with the exclusive regioselectivity (Entry 2). Among the various solvents, THF gave the highly regioselective fashion than DMSO (Entry 1, Entry 5), but it was only reproduced at the milligram scale process and Toluene or CH_2Cl_2 showed the decomposition of the precursor **103**

along with the trace amount of the oxocene **106** (Entry 3-4). Interestingly, the cyclization with dppm did not proceeded (Entry 6) and the cyclization with other ligands such as dppm, dppb, dppf or PPh_3 gave the opposite regioselectivity (Entry 7-9).

Table 6. Pd(0)-catalyzed cyclization of allylic acetate **103**



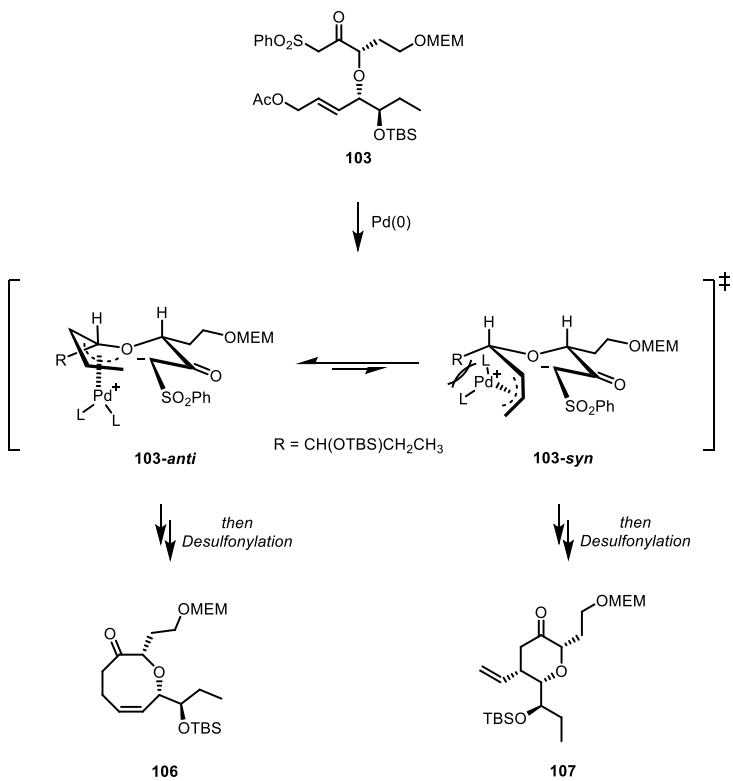
103 **106** **107**

Entry	Catalyst (3mol%)	Solvent	Yield	Ratio (**106** : **107**)
1	**$Pd(dppe)_2$**	DMSO	92%	4.2 : 1
2		**MeCN**	**95%**	**33 : 1**
3		Toluene	Trace	1 : 0
4		CH_2Cl_2		
5		THF	90%	28 : 1
6	$Pd_2(dppm)_3$		-	NR
7	$Pd(dppb)_2$		88%	1 : 2
8	$Pd(dppf)_2$		84%	1 : 3.3
9	$Pd(PPh_3)_4$		17%	0 : 1

Based on our results, we proposed a plausible mechanism for the excellent regioselective construction of the desired oxocene skeleton in **106** *via* Pd(0)-catalyzed cyclization reaction (**Figure 2**). The observed high regioselectivity for the endo-cyclic ring formation is presumably due to the difference of steric interaction between palladium π-allyl complex and the propyl side chain containing silyl ether group in the precursor **103**. Pd(0)-catalyzed cyclization proceeded through more favorable **103-*anti*** transition state with the least steric

repulsion than **103-*syn*** transition state possessing severe 1,2-interaction. Moreover, the deprotonation at β-ketosulfonyl moiety by the acetate anion of precursor **103** *via* cyclization is slower than carbonate anion and it can prolong the interconversion in transition state geometry.

Figure 2. Plausible mechanism for Pd(0)-catalyzed cyclization



For these reasons, the intramolecular allylic alkylation constructed the desired oxocene **106**, which was thermodynamically less preferred by entropic and enthalpic factors, with the exclusive regioselectivity. Interestingly, the tetrahydropyran **107** as minor regioisomer was obtained as a single diastereomer. Its newly generated stereocenter at the vinyl group at **107**, which could be *cis* or *trans* to the propyl side chain, was assigned as *cis* by NOESY

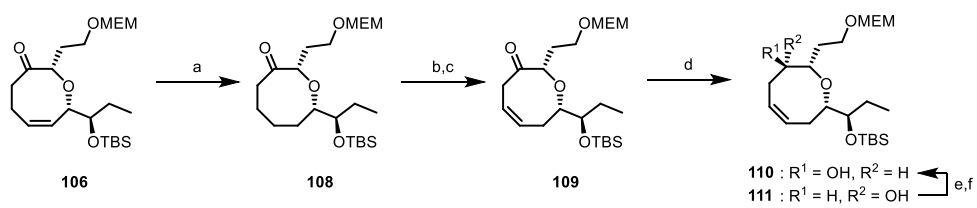
studies and this stereochemical result could be meaningfully supported the transition state geometry of our plausible mechanism to construct the key oxocene skeleton **106** with the highly regioselective fashion.

1-11. Deconjugative Isomerization and Diastereoselective Reduction

Having successfully constructed the oxocene **106**, we proceeded the sequential process to established the alcohol **110** as shown in **Scheme 19**. Catalytic hydrogenation of the oxocene **106** under the hydrogen atmosphere gave the oxocane **108**, which was smoothly converted to the ketone **109** through the combination of Saegusa oxidation with *in situ* deconjugative isomerization as the two-step process. In this process, we treated $Pd(OAc)_2$ to the silyl enol ether, which was obtained from the ketone **109** exposed to LiHMDS, TEA and TMSCl, followed by DBU without further purification.

The diastereoselective reduction of the ketone **109** using DIBAL-H in Toluene provided the desired *anti* alcohol **110** as major product, presumably *via* the substrate-controlled diastereoselective reduction, along with the separable minor diastereomer **111**, which could be converted to the desired *anti* alcohol **110** by Mitsunobu inversion.

Scheme 19. Deconjugative isomerization and diastereoselective reduction

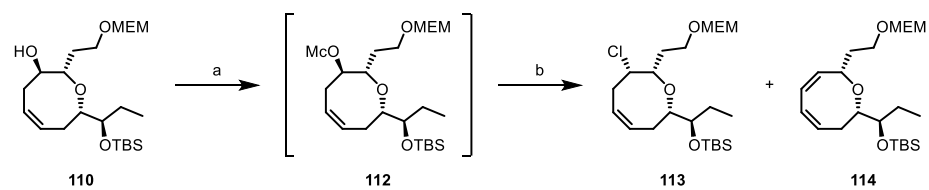


Reagents and conditions: (a) 10 wt% Pd/C, H_2, EtOAc/MeOH (3:1), rt, 100%; (b) LiHMDS, TMSCl, TEA, THF, -78 °C; (c) $Pd(OAc)_2$, MeCN, rt then DBU, rt, 91% for 2 steps; (d) DIBAL-H, toluene, rt, 81% for **110**, 17% for **111**; (e) DEAD, PPh_3, *p*-nitrobenzoic acid, THF, rt; (f) LAH, THF, 0 °C, 75% for 2 steps

1-12. Crucial Chlorination

Next, we turned our attention to the introduction of the crucial chloride at C(7) as shown in **Scheme 20**. To the best of our knowledge, the diastereoselective installation of the ring chlorine with the requisite alcohol **110** was not trivial because of the undesired elimination of the secondary hydroxyl group right after the chlorination under the Appel condition using CCl_4 and $P(Oct)_3$ at 80 ℃ and we also obtained only the undesired diene **114** using the same reaction condition. However, we could established the crucial chloro oxocene **113** through the modified procedure *via* the chloromethanesulfonate intermediate **112** with the minimal formation of the diene **114**.[30]

Scheme 20. Modified chlorination of *anti* alcohol **110**



110 **112** **113** **114**

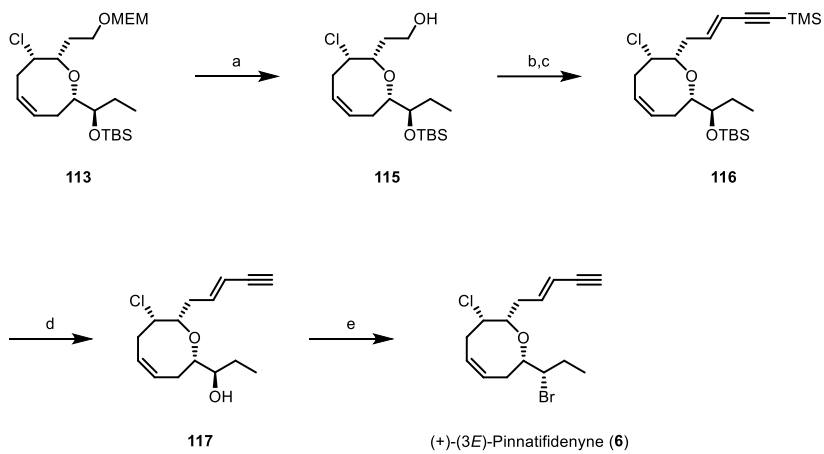
Reagents and conditions: (a) McCl, 2,6-lutidine, CH_2Cl_2, 0 °C; (b) LiCl, DMF, 35 °C, 71% for **113**, 18% for **114** for 2 steps

1-13. Completion of Total Synthesis of (+)-(3*E*)-Pinnatifidenyne (6)

For the completion of total synthesis of (+)-(3*E*)-Pinnatifidenyne (**6**), we first carefully carried out the deprotection of MEM group of the chloride **113** in the presence of $TiCl_4$ to afford the alcohol **115**, which was transformed into the (*E*)-enyne **116** *via* Dess-Martin oxidation and subsequent Wittig olefination of the resulting aldehyde with the exclusive (*E*)-selectivity.[31] Global deprotection of the silyl groups such as TMS and TBS with TBAF gave the alcohol **117** and the introduction of the bromide functionality at C(13) under the stand-

ard Appel condition with CBr_4 and $P(Oct)_3$ at the final stage successfully produced the (+)-(3*E*)-Pinnatifidenyne (**6**) in good yield.[32] The synthetic (**6**) was identical to the natural product in all aspects, including the spectral characteristics and optical rotation.[11a, 12]

Scheme 21. Completion of total synthesis of (+)-(3*E*)-Pinnatifidenyne (**6**)



Reagents and conditions: (a) $TiCl_4$, CH_2Cl_2, -78 °C to 0 °C, 92%; (b) DMP, CH_2Cl_2, rt; (c) (3-trimethyl silyl-2-propynyl)triphenylphosphonium bromide, *n*-BuLi, THF, -78 °C to 0 °C, 83% for 2 steps; (d) TBAF, THF, 0 °C to rt, 98%; (e) P(*n*-Oct)$_3$, CBr_4, toluene, 70 °C, 93%

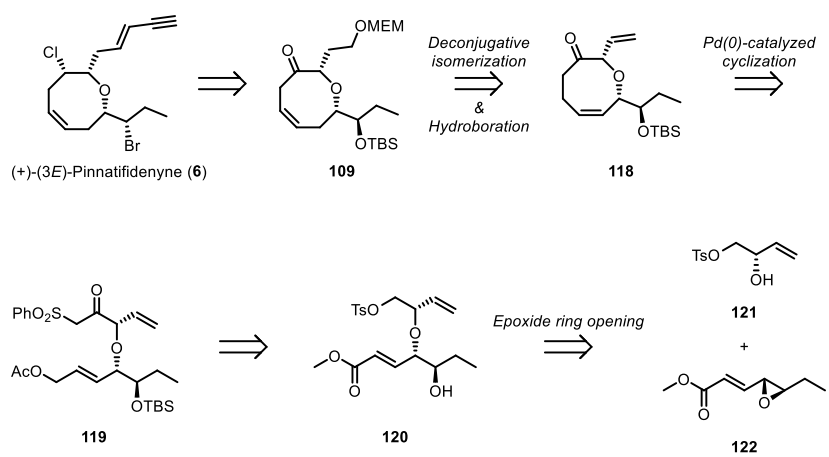
2. Synthetic Studies to Other Oxocene Natural Products

After the completion of (+)-(3*E*)-Pinnatifidenyne (**6**), we turned our attention to the efficient synthesis of the precursor for the Pd(0)-catalyzed cyclization. As we showed above, the ether linkage containing the cis-α,α'-orientation of the side chains was constructed by Evans aldol reaction using the chiral auxiliary moiety prepared from the optically active alcohol. Considering the more efficient strategy to construct the precursor with the desired ether linkage for the intramolecular Tsuji-Trost allylic alkylation, the epoxide ring opening could be the solution for our synthetic hurdle.

2-1. Regio- and Diastereoselective Epoxide Opening

To construct the precursor for the Pd(0)-catalyzed cyclization efficiently, we considered the opening reaction between the epoxide and the alcohol to provide the desired ether bond. Moreover, the application of Lewis acid-mediated epoxide opening by using the optically active vinyl epoxide and alcohol could control the regioselectivity and diastereoselectivity because the alcohol as a nucleophile could attack at the allylic position of the vinyl epoxide, which was activated by Lewis acid catalyst, *via* S_N2-type fashion. Based on these results, we envisioned the application of this convergent strategy to more unique and complicated marine natural products containing oxocene skeleton.

Scheme 22. Retrosynthetic analysis for convergent strategy



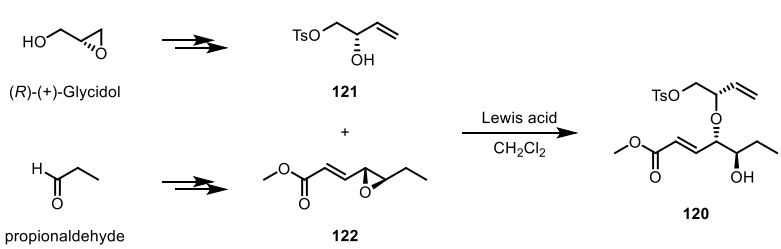
Our retrosynthetic plan is depicted in **Scheme 22**. For the syntheses of the diverse marine natural products containing oxocene skeleton including (+)-(3*E*)-Pinnatifidenyne (**6**), the oxocene **109** is the key and common intermediate which would be prepared from the ketone **118** by deconjugative isomerization and hydroboration. The oxocene skeleton of **118** would be constructed by regioselective Pd(0)-catalyzed cyclization, followed by desulfonylation

of the precursor **119**, which could be transformed from the alcohol **120** containing the desired *cis*-α,α'-substituted ether linkage. The alcohol **120** could be expected to be directly prepared from the known alcohol **121** and the known epoxide **122** through the regioselective epoxide ring opening reaction as the efficient convergent strategy.

2-2. Convergent Strategy for Pd(0)-Catalyzed Cyclization Precursor 119

The convergent strategy commenced with the preparation of two compounds such as the alcohol **121** and the epoxide **122**, which were conveniently transformed from the commercially available (*R*)-(+)-Glycidol and propionaldehyde by the simple modifications.[33] With the two compounds in hand, we performed the Lewis acid-mediated regioselective epoxide ring opening to construct the desired ether linkage with the cis-α,α'-orientation (**Table 7**).[34] Among the various reaction conditions, the epoxide ring opening with $BF_3 \cdot OEt_2$ afforded the alcohol **120** with the best result in 80% yield along with minimal decomposition of the epoxide **122**. Interestingly, most of Lewis acids could not progress the opening reaction and $Cu(OTf)_2$ showed the only decomposition of the epoxide **122**.

Table 7. Lewis acid-mediated regioselective epoxide ring opening

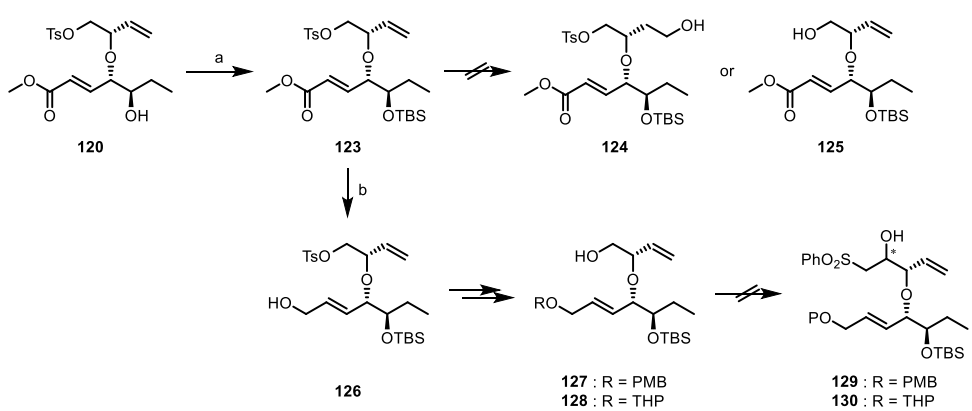


Entry	Lewis acid (5mol%)	Temperature	Result
1	**$BF_3 \cdot OEt_2$**	0 ℃ to rt	15%
2		**rt to 35 ℃**	**80%**

3	$Cu(OTf)_2$	0 ℃ to rt	Decomposition of epoxide
4	$La(OTf)_3$		NR
5	$Zn(OTf)_2$		
6	$Yb(OTf)_3$		
7	$Sc(OTf)_3$		20% (w/ Decomposition of epoxide)

Having successfully afforded the alcohol **120**, we conducted the preparation of the precursor for Pd(0)-catalyzed cyclization as shown in **Scheme 23**. TBS protection of the alcohol **120** produced smoothly the ester **123** and we envisioned the hydroboration of the terminal olefin or the removal of tosyl group of the ester **123**, however, both of them could not proceeded. For these reasons, the ester **123** was reduced with DIBAL-H to give the allylic alcohol **126**, which was converted to the alcohol **127** or **128** by the protection. To our surprise and disappointment, Dess-Martin oxidation of the alcohol, followed by the alkylation with the methyl phenyl sulfone of the resulting aldehyde could not afford the desired secondary alcohol **129** or **130**.

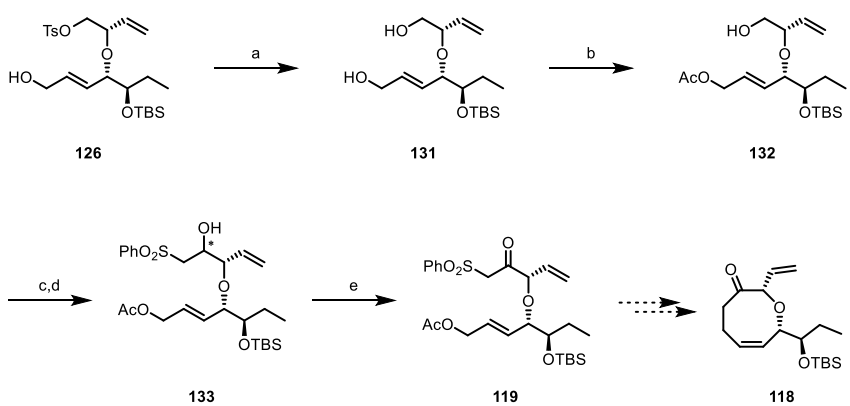
Scheme 23. Approaches to the precursor for cyclization



Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 93%; (b) DIBAL-H, CH_2Cl_2, 0 °C, 98%

Nevertheless, we could obtain the proper ester **123** containing the desired ether linkage *via* the regioselective epoxide ring opening in a highly convergent manner. With this ester **123** in hand, we suggested the revised synthetic route for the precursor **119** as shown in **Scheme 24**. Removal of tosyl group of the ester **126** with 5% Na/Hg, followed by the chemoselective acetylation of the resulting diol **131** gave the alcohol **132**. Although we investigated the chemoselective acetylation of the allylic alcohol of the diol **131** under the various reaction conditions including base and temperature, the desired alcohol **132** was just obtained in moderate yield along with the diacetate byproduct. Dess-Martin oxidation of the alcohol **132** and the alkylation with the anion of methyl phenyl sulfone to the resulting aldehyde provided the secondary alcohol **133**. Finally, the precursor **119** was achieved by the oxidation of the secondary alcohol **133**.

Scheme 24. Preparation of Pd(0)-catalyzed cyclization precursor **119**



Reagents and conditions: (a) 5% Na/Hg, Na_2HPO_4, MeOH, rt, 96%; (b) Ac_2O, pyridine, DMAP, CH_2Cl_2, -10 °C, 55%; (c) DMP, $NaHCO_3$, CH_2Cl_2, rt; (d) methyl phenyl sulfone, *n*-BuLi, THF, -78 °C, 94% for 2 steps; (e) DMP, $NaHCO_3$, CH_2Cl_2, rt, 100%

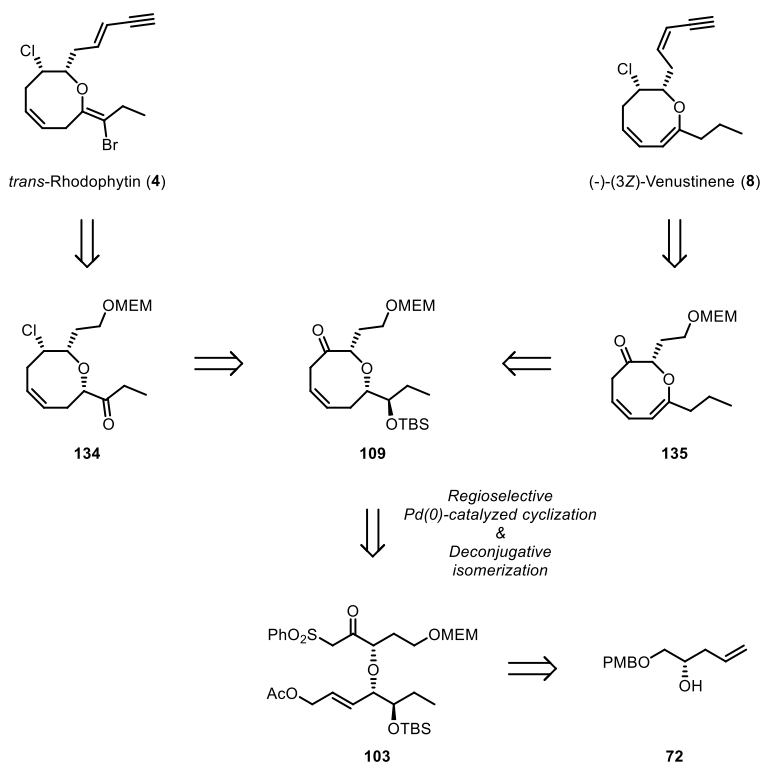
With the precursor **119** in hand, we performed the regioselective Pd(0)-catalyzed cycli-

zation under the previously optimized conditions from the total synthesis of (+)-(3*E*)-Pinnatifidenyne (**6**). We could not produce the oxocene **118** yet, however, we continue to attempt to establish the convergent strategy to construct the desired oxocene skeleton.

2-3. Retrosynthetic Analysis of Other Congeners

In this connection, we turned our attention to the synthetic application for the more complicated marine natural products containing the oxocene skeleton, especially, with the requisite side chains of the Laurenan type framework. The retrosynthetic analysis for other congeners such as *trans*-Rhodophytin (**4**) and (-)-(3*Z*)-Venustinene (**8**) based on our synthetic strategy is outlined in **Scheme 25**.[6, 7b, 13]

Scheme 25. Retrosynthetic analysis of other congeners

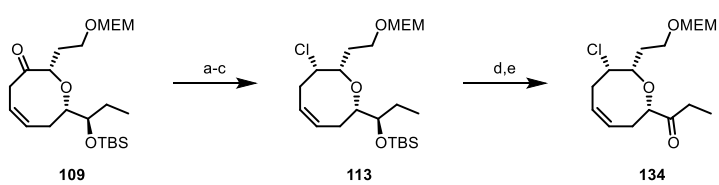


We expected theses congeners could be afforded from the oxocene **109**, as the key intermediate, which was derived from the precursor **103** by the regioselective Pd(0)-catalyzed cyclization and deconjugative isomerization. First, the *exo*-vinyl bromide as the unique moiety of *trans*-Rhodophytin (**4**) could be provided from the ketone **134**, which would be prepared from the key intermediate **109** by the diastereoselective chlorination, desilylation and oxidation of the resulting alcohol. Second, (-)-(3*Z*)-Venustinene (**8**) could be prepared from the ketone **135** by the diastereoselective chlorination and (*Z*)-selective enyne formation. The inside diene as the unique moiety of the ketone **135** would also be prepared from the key intermediate **109** by the desilylation, mesylation of the resulting alcohol and elimination.

2-4. Synthetic Approaches for *trans*-Rhodophytin (4)

The synthesis commenced with the preparation of the ketone **134** as shown in **Scheme 26**. Diastereoselective reduction of the ketone **109**, followed by the modified chlorination of the resulting *anti* alcohol *via* the chloromethanesulfonyl intermediate provided the chloride **113**, which was transformed into the ketone **134** through the removal of the silyl group with TBAF and the subsequent Dess-Martin oxidation of the resulting alcohol.

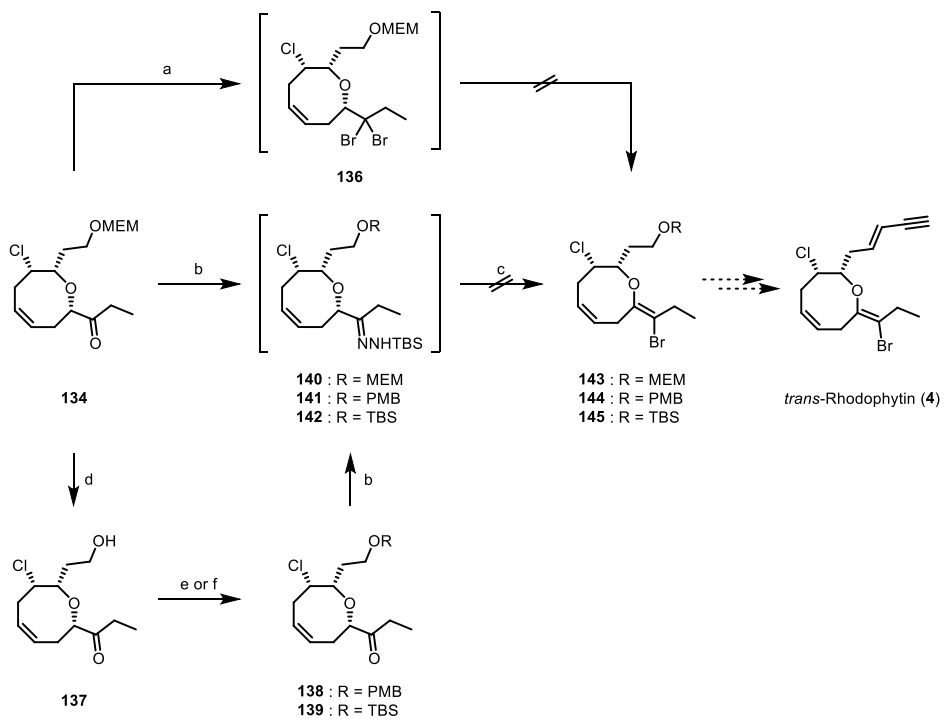
Scheme 26. Preparation of the ketone **134**



Reagents and conditions: (a) DIBAL-H, toluene, rt, 81% (b) McCl, 2,6-lutidine, CH_2Cl_2, 0 °C; (c) LiCl, DMF, 35 °C, 71% for 2 steps; (d) TBAF, THF, 0 °C to rt, 100%; (e) DMP, CH_2Cl_2, rt, 95%

With the ketone **134** in hand, we investigated the introduction of the *exo*-vinyl bromide as the unique moiety in *trans*-Rhodophytin (**4**) as shown in **Scheme 27**. Among the various attempts based on the model study, we applied the more reactive reaction conditions to the ketone **134**.

Scheme 27. Approaches to the *exo*-vinyl bromide moiety



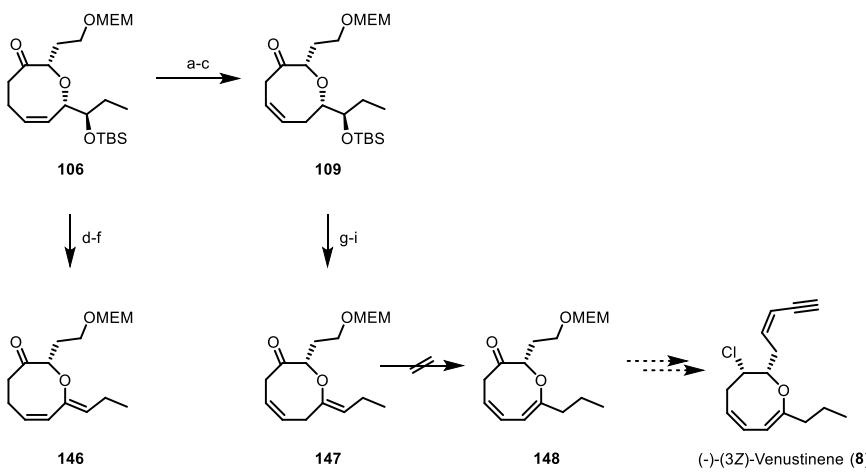
Reagents and conditions: (a) $(PhO)_3P$, Br_2, TEA, CH_2Cl_2, -78 °C, decomposed; (b) TBSHNNHTBS, $Sc(OTf)_3$, $CHCl_3$, rt; (c) Br_2, BTMG, CH_2Cl_2, 0 °C to rt; (d) $TiCl_4$, CH_2Cl_2, 0 °C, 97%; (e) benzyl 2,2,2-trichloroacetimidate, PTSA, CH_2Cl_2, 0 °C to rt, 100% for **138**; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95% for **139**

First, we attempted to produce the *exo*-vinyl bromide **143** *via* the *gem*-dibromide **136**, however, this reaction condition showed only the decomposition of the ketone **134** without

the desired product.[35] Next, we performed to afford the *exo*-vinyl bromide moiety *via* the hydrazone intermediate **140** by the modified Wolff-Kishner reduction.[36] The ketone **134** was disappeared under this condition to provide the hydrazone intermediate **140**, but the *exo*-vinyl bromide **143** could not be produced *via* Barton synthesis with Br_2 and the hindered guanidine base. Interestingly, the inside double bond was disappeared and we assumed the oxygen atom of the oxocene core attacked the inside double bond, which was activated by the induced bromonium ion. The ketone **138** or **139**, containing the other protecting group instead of MEM group of the ketone **134**, disappointingly showed the same result.

2-5. Synthetic Approaches for (-)-(3*Z*)-Venustinene (8)

Scheme 28. Approaches to the inside diene moiety



Reagents and conditions: (a) 10 wt% Pd/C, H_2, EtOAc/MeOH (3:1), rt, 100%; (b) LiHMDS, TMSCl, TEA, THF, -78 °C; (c) $Pd(OAc)_2$, MeCN, rt then DBU, rt, 91% for 2 steps; (d) TBAF, THF, rt, 100%; (e) MsCl, TEA, CH_2Cl_2, 0 °C, 95%; (f) DBU, toluene, 60 °C, 98%; (g) TBAF, THF, rt, 100%; (h) MsCl, TEA, CH_2Cl_2, 0 °C, 92%; (i) DBU, toluene, 60 °C, 95%;

Next, we investigated the installation of the inside diene moiety of (-)-(3*Z*)-Venustinene (**8**). Removal of the silyl group of key intermediate **109** with TBAF and mesylation of the resulting alcohol, followed by the elimination with DBU provided the ketone **147**. With the ketone **147** in hand, we performed the migration of the *exo*-olefin to the inside of the ring to construct the diene moiety under the various basic conditions, however, this base promoted isomerization did not happen. Interestingly, this elimination established the olefin at the *exo*-position of the ring and the ketone **106** showed the same fashion to the *exo*-position.

Based on these trials and errors, we continue to attempt to synthesize the unique and more complicated marine natural products and establish the efficient and general strategy for the oxocene natural products from *Laurencia* species, especially, containing the Laurenan type framework.

III. Conclusion

We have achieved the asymmetric total synthesis of (+)-(3*E*)-Pinnatifidenyne (**6**). The key features of our synthesis involve the highly regioselective intramolecular Tsuji-Trost allylic alkylation and the sequential *in situ* deconjugative isomerization to construct the *cis*-α,α'-disubstituted oxocene skeleton, containing the well-known difficulty of its development due to thermodynamically unfavorable entropic and enthalpic factors. In addition, we efficiently elaborated the crucial chloride functionality, which was synthetic hurdle because of the undesired elimination, through the modified chlorination *via* the chloromethanesulfonate intermediate, mediated by the substrate-controlled diastereoselective reduction. Finally, the introduction of (*E*)-enyne and the bromide functionality at the final stage, successfully completed the total synthesis of the (+)-(3*E*)-Pinnatifidenyne (**6**).

In this connection, we efficiently synthesized the precursor for Pd(0)-catalyzed cyclization. Our convergent synthetic strategy involves Lewis acid-mediated epoxide opening using the optically active vinyl epoxide and alcohol *via* S_N2-type fashion. Based on these studies, we envision our unified synthetic strategy can widely apply to more unique and complicated marine natural products containing oxocene skeleton from *Laurencia* species, especially, with the halogen atoms and the requisite side chains like the Laurenan type framework.

IV. Experimental Section

General Experimental Procedure

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, chloroform, triethylamine, acetonitrile and pyridine were freshly distilled from calcium hydride. All solvents used for routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried at 100 ℃. Air and moisture sensitive reactions were performed under argon atmosphere. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck). Optical rotations were measured with JASCO P-2000 digital polarimeter at ambient temperature using 10 mm cell of 0.2 mL capacity. Infrared spectra were recorded on JASCO FT/IR-4200 spectrometer. High resolution mass spectra were obtained with JEOL JMS-700 or Agilent Q-TOF 6530 MS. ^{1}H and ^{13}C NMR spectra were recorded on either Bruker Avance 500 or Bruker Avance III HD 800 MHz-spectrometer with a 5mm CPTCI cryoprobe as solutions in deuteriochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CHCl_3$). ^{1}H-NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; dd, doublet of doublet; dt, doublet of triplet; ddd, doublet of doublet of doublet; dqd, doublet of quartet of doublet; t, triplet; td, triplet of doublet; q, quartet; qd, quartet of doublet; quint, quintet; br, broad; m, multiplet and/or multiple resonance), number of protons, and coupling constant in hertz (Hz).

(*R*)-4-benzyl-3-(2-(((*S*)-1-((4-methoxybenzyl)oxy)pent-4-en-2-yl)oxy)acetyl)oxazolidin-2-one (73). To a suspension of 60% sodium hydride (2.98 g, 74.5 mmol) in THF (150 mL) was added dropwise a solution of iodoacetic acid (6.93 g, 37.3 mmol) in THF (40 mL) at 0 ℃ and the reaction mixture was warmed to ambient temperature. After stirring for 1 h, a solution of alcohol **72** (5.52 g, 24.8 mmol) in THF (25 mL) was added at 0 ℃ and stirred for 2 h at 50 ℃. The resulting mixture was cooled to 0 ℃, slowly quenched with H_2O (100 mL) and washed with Et_2O (150 mL). After the aqueous layer was cooled to 0 ℃, carefully acidified with 1N HCl (50 mL) and extracted with EtOAc (100 mL × 2). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of crude acid in THF (50 mL) were added triethylamine (3.81 mL, 27.3 mmol) and the reaction mixture was cooled to -78 ℃. Pivaloyl chloride (3.36 ml, 27.3 mmol) was added dropwise and warmed to 0 ℃, where it was stirred for 1 h and subsequently cooled to -78 ℃. To a solution of (*R*)-4-benzyl-2-oxazolidinone (5.72 g, 32.3 mmol) in THF (100 mL) was slowly added *n*-BuLi (11.9 mL, 2.5 M in *n*-hexane, 29.8 mmol) and stirred for 30 min. The lithiated oxazolidinone was added to the mixed anhydride by cannulation at -78 ℃, and stirred for additional 15 min. The reaction mixture was stirred at 0 ℃ for 1 h, quenched with H_2O (150 mL) and extracted with EtOAc (100 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:3) to afford oxazolidinone **73** (10.1 g, 93%) as a colorless oil: $[\alpha]_D^{25}$ -47.30 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.30 (t, 2H, *J* = 7.2 Hz), 7.26-7.24 (m, 3H), 7.16 (d, 2H, *J* = 7.0 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 5.90-5.83 (m, 1H), 5.10 (dd, 1H, *J* = 17.1 Hz, *J* = 1.5), 5.06 (d, 1H, *J* = 10.2 Hz), 4.85 (d, 2H, *J* = 1.3 Hz), 4.62-4.57 (m, 1H), 4.45 (s, 2H), 4.18-4.12 (m, 2H), 3.77 (s, 3H), 3.75-3.70 (m, 1H), 3.60-3.52 (m, 2H), 3.28 (dd, 1H, *J* = 13.4 Hz, *J* = 3.1 Hz), 2.64 (dd, 1H, *J* = 13.4 Hz, *J* = 9.7 Hz), 2.43-2.35 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.5, 159.1, 153.3, 135.0,

134.2, 130.2, 129.3, 129.1, 128.9, 127.3, 117.3, 113.7, 78.9, 72.9, 72.4, 69.9, 67.1, 55.2, 54.7, 37.6, 36.3; IR (neat) ν_{max} 2918, 2861, 1781, 1718, 1613, 1513, 1455, 1393, 1351, 1249, 1218, 1135, 1032, 920, 822, 770, 702 cm^{-1}; LR-MS (FAB) *m/z* 438 ($M-H^+$); HR-MS (FAB) calcd for $C_{25}H_{28}NO_6$ ($M-H^+$) 438.1917, found 438.1910.

(*R*)-4-benzyl-3-((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-(((*S*)-1-((4-methoxybenzyl)oxy)pent-4-en-2-yl)oxy)pentanoyl)oxazolidin-2-one (71). To a solution of oxazolidinone **73** (4.81 g, 10.9 mmol) in CH_2Cl_2 (110 mL) was added dropwise *n*-Bu_2BOTf (12.0 mL, 1.0 M solution in CH_2Cl_2, 12.0 mmol) and triethylamine (1.83 mL, 13.1 mmol) at -78 ℃. The reaction mixture was warmed to -40 ℃, stirred for additional 30 min and cooled to -78 ℃. Propionaldehyde (0.956 mL, 13.1 mmol) was added dropwise and stirred for 1 h at the same temperature. The reaction mixture was rapidly warmed to 0 ℃, stirred for additional 1 h and quenched with a saturated NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (100 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:3) to afford aldol adduct (3.92 g, 72%) as a colorless oil: $[\alpha]_D^{25}$ +12.34 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.31 (t, 2H, *J* = 7.1 Hz), 7.24-7.20 (m, 3H), 7.08 (d, 2H, *J* = 7.3 Hz), 6.85 (d, 2H, *J* = 8.5 Hz), 5.88-5.80 (m, 1H), 5.34 (d, 1H, *J* = 2.2 Hz), 5.11 (dd, 2H, *J* = 18.3 Hz, *J* = 10.4 Hz), 4.52-4.49 (m, 1H), 4.40 (q, 2H, J_{AB} = 11.6 Hz), 4.08 (t, 1H, *J* = 8.3 Hz), 3.95 (dd, 1H, *J* = 9.1 Hz, *J* = 2.0 Hz), 3.78 (s, 3H), 3.76-3.74 (m, 1H), 3.69 (t, 1H, *J* = 5.6 Hz), 3.64 (dd, 1H, *J* = 10.3 Hz, *J* = 7.5 Hz), 3.45 (dd, 1H, *J* = 10.4 Hz, *J* = 3.1 Hz), 3.25 (dd, 1H, *J* = 13.3 Hz, *J* = 2.7 Hz), 2.41-2.29 (m, 2H), 1.94 (dd, 1H, *J* = 13.1 Hz, *J* = 11.0 Hz), 1.63 (quint, 2H, *J* = 7.2 Hz), 0.99 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 171.4, 159.1, 153.5, 135.6, 134.2, 130.2, 129.3, 128.8, 128.7, 127.1, 117.9, 113.7, 80.2, 79.9, 74.3, 73.4, 72.7, 66.7, 55.7, 55.2, 37.0, 36.4, 27.1, 10.1; IR (neat) ν_{max} 3517, 2932, 1778, 1713, 1613, 1513, 1455, 1391, 1355, 1247, 1212, 1140, 1107, 1033, 920, 820, 764, 702 cm^{-1}; LR-MS (FAB) *m/z* 496 ($M-H^+$); HR-MS (FAB)

calcd for $C_{28}H_{34}NO_7$ ($M\text{-}H^+$) 496.2336, found 496.2343.

To a solution of aldol adduct (4.53 g, 9.10 mmol) in CH_2Cl_2 (45 mL) was added dropwise 2,6-lutidine (3.17 mL, 27.3 mmol) and TBSOTf (3.14 mL, 13.7 mmol) at 0 ℃. After stirring for 1 h, the reaction mixture was quenched with H_2O (30 mL) and extracted with CH_2Cl_2 (40 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:5) to afford silyl ether **71** (5.29 g, 95%) as a colorless oil: $[\alpha]_D^{25}$ -5.36 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.29 (t, 2H, *J* = 7.3 Hz), 7.23-7.20 (m, 3H), 7.12 (d, 2H, *J* = 7.2 Hz), 6.82 (d, 2H, *J* = 8.7 Hz), 5.88-5.83 (m, 1H), 5.42 (d, 1H, *J* = 3.5 Hz), 5.09 (d, 1H, *J* = 16.7 Hz), 5.05 (d, 1H, *J* = 10.1 Hz), 4.46-4.44 (m, 1H), 4.42 (d, 2H, *J* = 4.1 Hz), 4.04-3.99 (m, 2H), 3.94-3.91 (m, 1H), 3.75 (s, 3H), 3.67-3.64 (m, 1H), 3.60 (dd, 1H, *J* = 10.2 Hz, *J* = 6.7 Hz), 3.44 (dd, 1H, *J* = 10.3 Hz, *J* = 3.6 Hz), 3.28 (dd, 1H, *J* = 13.2 Hz, *J* = 2.6 Hz) 2.40-2.29 (m, 2H), 2.14 (dd, 1H, *J* = 13.1 Hz, *J* = 10.7 Hz), 1.87-1.81 (m, 1H), 1.48-1.42 (m, 1H), 0.92 (t, 3H, *J* = 7.5 Hz), 0.83 (s, 9H), 0.00 (d, 6H, *J* = 16.2 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 171.6, 159.0, 153.3, 135.8, 134.5, 130.6, 129.4, 128.9, 128.8, 127.1, 117.3, 113.7, 79.9, 79.2, 74.7, 72.9, 72.8, 66.4, 56.3, 55.2, 37.2, 36.4, 26.3, 25.8, 18.0, 10.2, -4.3, -4.6; IR (neat) ν_{max} 2930, 2857, 1781, 1714, 1613, 1514, 1464, 1386, 1349, 1249, 1209, 1105, 1037, 918, 837, 733, 702 cm^{-1}; LR-MS (FAB) *m/z* 610 ($M\text{-}H^+$); HR-MS (FAB) calcd for $C_{34}H_{48}NO_7Si$ ($M\text{-}H^+$) 610.3200, found 610.3203.

(*R*)-4-benzyl-3-((10*S*,12*R*)-12-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)propyl)-10-(((4-methoxybenzyl)oxy)methyl)-2,5,7,11-tetraoxatridecan-13-oyl)oxazolidin-2-one (87). To a solution of silyl ether **71** (4.42 g, 7.22 mmol) in *t*-BuOH (35 mL), THF (35 mL) and H_2O (7 mL) was added NMO (1.06 g, 9.03 mmol) and OsO_4 (3.61 mL, 0.1 M solution in toluene, 0.361 mmol) and stirred for 12 h. The reaction mixture was cooled to 0 ℃, $NaIO_4$ (3.86 g, 18.1 mmol) was added and warmed to ambient temperature. After stirring for 1 h, the

reaction mixture was quenched with H_2O (40 mL) and extracted with EtOAc (50 mL × 2). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of crude aldehyde in THF (75 mL) was added BH_3·THF (7.22 mL, 1.0 M solution in THF, 7.22 mmol) at 0 ℃ and stirred for 1 h. The reaction mixture was quenched with H_2O (40 mL) and extracted with EtOAc (50 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:2) to afford alcohol (3.36 g, 79%) as a colorless oil: $[\alpha]_D^{25}$ +1.68 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.29 (t, 2H, *J* = 7.3 Hz), 7.23-7.21 (m, 1H), 7.18 (d, 1H, *J* = 8.6 Hz), 7.09 (d, 2H, *J* = 7.1 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 5.42 (d, 1H, *J* = 1.7 Hz), 4.42-4.35 (m, 3H), 3.99 (t, 1H, *J* = 7.5 Hz), 3.98-3.92 (m, 2H), 3.88 (t, 1H, *J* = 6.8 Hz), 3.86-3.81 (m, 2H), 3.78 (s, 3H), 3.71 (dd, 1H, *J* = 7.9 Hz), 3.41-3.37 (m, 2H), 3.24 (dd, 1H, *J* = 13.2 Hz, *J* = 2.7 Hz), 1.86-1.75 (m, 4H), 1.65-1.56 (m, 1H), 1.00 (t, 3H, *J* = 7.5 Hz), 0.85 (s, 9H), -0.00 (s, 3H), -0.09 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.9, 158.9, 153.2, 135.7, 130.0, 129.2, 128.7, 128.4, 127.0, 113.6, 80.7, 79.7, 74.3, 74.1, 72.6, 66.3, 60.5, 56.1, 55.1, 36.5, 34.1, 27.2, 25.5, 17.7, 10.1, -4.5, -5.2; IR (neat) ν_{max} 3516, 2931, 2858, 1781, 1719, 1613, 1514, 1464, 1388, 1350, 1249, 1199, 1148, 1104, 1035, 938, 836, 702 cm^{-1}; LR-MS (FAB) *m/z* 616 ($M+H^+$); HR-MS (FAB) calcd for $C_{33}H_{50}NO_8Si$ ($M+H^+$) 616.3306, found 616.3307.

To a solution of alcohol (4.72 g, 7.66 mmol) in CH_2Cl_2 (120 mL) were added K_2CO_3 (4.56 g, 33.0 mmol) and diisopropylethylamine (6.33 mL, 38.3 mmol) at ambient temperature. The reaction mixture was cooled to 0 ℃ and carefully added MEMCl (3.76 mL, 33.0 mmol) with bubbling of Ar gas. After stirring for 1 h at the same temperature, the reaction mixture was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (70 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-

hexane = 1:3) to afford ether **87** (5.18 g, 96%) as a colorless oil: $[\alpha]_D^{25}$ +2.53 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.28 (t, 2H, *J* = 7.3 Hz), 7.22-7.19 (m, 3H), 7.12 (d, 2H, *J* = 7.2 Hz), 6.83 (d, 2H, *J* = 8.5 Hz), 5.43 (d, 1H, *J* = 3.2 Hz), 4.70 (s, 2H), 4.44-4.37 (m, 3H), 4.02-3.94 (m, 2H), 3.94-3.89 (m, 1H), 3.84-3.79 (m, 1H), 3.77 (s, 3H), 3.72-3.67 (m, 3H), 3.67-3.61 (m, 2H), 3.53 (t, 2H, *J* = 4.6 Hz), 3.41 (dd, 1H, *J* = 10.5 Hz, *J* = 3.1 Hz), 3.37 (s, 3H), 3.28 (dd, 1H, *J* = 13.3 Hz, *J* = 2.6 Hz), 2.10-1.95 (m, 1H), 1.91-1.75 (m, 3H), 1.50-1.43 (m, 2H), 0.93 (t, 3H, *J* = 7.6 Hz), 0.83 (s, 9H), -0.01 (s, 3H), -0.03 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 171.5, 158.9, 153.1, 135.8, 130.4, 129.3, 128.8, 127.0 113.6, 95.4, 79.5, 77.5, 74.6, 73.8, 72.6, 71.7, 66.7, 66.2, 64.2, 58.9, 56.2, 55.1, 36.9, 32.1, 26.3, 25.8, 17.9, 10.1, -4.4, -4.7; IR (neat) ν_{max} 2930, 2882, 1781, 1717, 161, 1514, 1464, 1386, 1350, 1249, 1209, 1197, 1103, 1038, 939, 837, 732, 703 cm^{-1}; LR-MS (FAB) *m/z* 702 ($M-H^+$); HR-MS (FAB) calcd for $C_{34}H_{56}NO_{10}Si$ ($M-H^+$) 702.3674, found 702.3683.

Ethyl (10*S*,12*S*,*E*)-12-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)propyl)-10-(((4-methoxybenzyl)oxy)methyl)-2,5,7,11-tetraoxapentadec-13-en-15-oate (86). To a solution of ether **87** (3.52 g, 5.00 mmol) in Et_2O (50 mL) was added MeOH (0.405 mL, 10.0 mmol) and cooled to 0 ℃. $LiBH_4$ (7.50 mL, 2.0 M solution in THF, 15.0 mmol) was added dropwise and stirred for 1 h at the same temperature. The reaction mixture was quenched with Rochelle solution (50 mL) and extracted with EtOAc (50 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:2) to afford alcohol (2.57 g, 97%) as a colorless oil: $[\alpha]_D^{25}$ -16.59 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.23 (d, 2H, *J* = 9.1 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 4.66 (d, 2H, *J* = 2.1 Hz), 4.47 (s, 2H), 3.78 (s, 4H), 3.71 (dd, 1H, *J* = 11.5 Hz, *J* = 2.7 Hz), 3.69-3.64 (m, 1H), 3.64-3.58 (m, 3H), 3.58-3.54 (m, 2H), 3.54-3.48 (m, 4H), 3.40 (dd, 1H, *J* = 10.0 Hz, *J* = 7.3 Hz), 1.77-1.71 (m, 1H), 1.69-1.60 (m, 2H), 0.89-0.86 (m, 12H), 0.04 (d, 6H, *J* = 4.4 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 159.3, 129.4, 113.7, 95.3, 83.0, 76.0, 73.9, 73.0, 72.5, 71.7, 66.7, 63.9, 61.5,

58.9, 55.1, 32.8, 25.7, 24.3, 17.9, 10.8, -4.5, -4.8; IR (neat) ν_{max} 3470, 2955, 2882, 1613, 1515, 1465, 1251, 1175, 1112, 939, 836, 795, 727, 680 cm^{-1}; LR-MS (FAB) *m/z* 531 ($M+H^+$); HR-MS (FAB) calcd for $C_{27}H_{51}O_8Si$ ($M+H^+$) 531.3353, found 531.3359.

To a solution of alcohol (2.45 g, 4.62 mmol) in CH_2Cl_2 (50 mL) was added $NaHCO_3$ (1.16 g, 13.8 mmol) and Dess-Martin periodinane (3.92 g, 9.23 mmol) at ambient temperature. After stirring for 4 h, the reaction mixture was quenched with a saturated $Na_2S_2O_3$ solution (50 mL) at 0 ℃ and extracted with CH_2Cl_2 (50 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of *t*-BuOK (0.777 g, 6.92 mmol) in THF (70 mL) was added dropwise triethyl phosphonoacetate (1.37 mL, 6.92 mmol) at 0 ℃ and stirred for 1h. The ylide was added to a solution of crude aldehyde in THF (50 mL) by cannulation at 0 ℃ and stirred for 1 h. The reaction mixture was quenched with H_2O (50 mL) at 0 ℃ and extracted with EtOAc (70 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:3) to afford ester **86** (2.65 g, 96%) as a colorless oil: $[\alpha]_D^{25}$ -40.90 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.20 (d, 2H, *J* = 8.6 Hz), 6.99 (dd, 1H, *J* = 15.7 Hz, *J* = 4.3 Hz), 6.83 (d, 2H, *J* = 8.6 Hz), 6.12 (dd, 1H, *J* = 15.7 Hz, *J* = 1.5 Hz), 4.67 (d, 2H, *J* = 3.0 Hz), 4.39 (q, 2H, J_{AB} = 11.7 Hz), 4.21-4.14 (m, 2H), 4.14-4.10 (m, 1H), 3.78 (s, 3H), 3.71-3.65 (m, 2H), 3.65-3.59 (m, 3H), 3.59-3.54 (m, 1H), 3.52 (t, 2H, *J* = 4.7 Hz), 3.44-3.39 (m, 2H), 3.37 (s, 3H), 1.82-1.71 (m, 2H), 1.51-1.49 (m, 1H), 1.27 (t, 3H, *J* = 7.1 Hz), 1.22-1.16 (m, 1H), 0.87 (s, 9H), 0.85 (t, 3H, *J* = 7.2 Hz), 0.04 (d, 6H, *J* = 3.8 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 166.4, 159.0, 146.3, 130.2, 129.1, 121.7, 113.6, 95.4, 80.5, 75.1, 74.4, 72.9, 72.7, 71.7, 66.7, 64.0, 60.0, 58.9, 55.1, 32.1, 25.7, 24.7, 17.9, 14.1, 10.4, -4.5, -4.8; IR (neat) ν_{max} 2930, 2881, 1720, 1657, 1613, 1514, 1465, 1365, 1302, 1251, 1047, 836, 794, 729, 667 cm^{-1}; LR-MS (FAB) *m/z* 531 ($M-H^+$); HR-MS (FAB) calcd for $C_{31}H_{53}O_9Si$ ($M-H^+$) 597.3459, found 597.3460.

(4*S*,5*R*,*E*)-4-(((*S*)-13-(4-methoxyphenyl)-2,5,7,12-tetraoxatridecan-10-yl)oxy)hept-2-ene-1,5-diol (104). To a solution of ester **86** (1.93 g, 3.22 mmol) in THF (30 mL) was added TBAF (4.83 mL, 1.0 M solution in THF, 4.83 mmol) at ambient temperature and stirred for 2 h at the same temperature. The reaction mixture was quenched with a saturated NH_4Cl solution (20 mL) and extracted with EtOAc (30 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:1) to afford alcohol (1.56 g, 100%) as a colorless oil: $[\alpha]_D^{25}$ +3.38 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.20 (d, 2H, *J* = 8.5 Hz), 6.85-6.81 (m, 3H), 6.08 (d, 1H, *J* = 15.8 Hz), 4.68 (s, 2H), 4.38 (q, 2H, J_{AB} = 11.6 Hz), 4.20-4.14 (m, 2H), 3.84 (t, 1H, *J* = 7.0 Hz), 3.78 (s, 3H), 3.76-3.70 (m, 2H), 3.66 (q, 2H, *J* = 4.2 Hz), 3.64-3.58 (m, 1H), 3.52 (t, 2H, *J* = 4.5 Hz), 3.50 (br, 1H), 3.43-3.37 (m, 3H), 3.36 (s, 3H), 1.90-1.75 (m, 2H), 1.54-1.46 (m, 1H), 1.41-1.30 (m, 1H), 1.26 (t, 3H, *J* = 7.2 Hz), 0.95 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 166.1, 159.2, 145.7, 130.1, 129.3, 123.2, 113.7, 95.3, 82.3, 76.5, 74.9, 73.0, 72.1, 71.7, 67.0, 64.3, 60.5, 59.0, 55.2, 31.5, 25.4, 14.2, 9.8; IR (neat) ν_{max} 3470, 2933, 2878, 1718, 1657, 1613, 1586, 1514, 1465, 1367, 1303, 1249, 1175, 1100, 1038, 982, 849, 882 cm^{-1}; LR-MS (ESI) *m/z* 502 ($M+NH_4^+$); HR-MS (ESI) calcd for $C_{25}H_{44}NO_9$ ($M+NH_4^+$) 502.3016, found 502.2979.

To a solution of alcohol (1.54 g, 3.18 mmol) in THF (6 mL) was added *p*-nitrobenzoic acid (1.06 g, 6.36 mmol), PPh_3 (1.67 g, 6.36 mmol) and DEAD (3.18 mL, 2.2 M solution in toluene, 6.99 mmol) at 0 ℃ and sonicated for 30 min at the ambient temperature. The reaction mixture was directly filtered through a short column of silica gel (EtOAc:*n*-hexane = 1:2) to afford a crude *p*-nitrobenzoate. The residue was used in the next step without further purification. To a solution of crude *p*-nitrobenzoate in THF (35 mL) was added dropwise a solution of LAH (15.9 mL, 1.0 M solution in Et_2O, 15.9 mmol) in THF (mL) at 0 ℃. After stirring for 1 h at the same temperature, the reaction mixture was quenched with

Rochelle solution (50 mL) and extracted with EtOAc (50 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 2:1) to afford diol **104** (1.10 g, 78%) as a colorless oil: $[\alpha]_D^{25}$ -3.92 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.22 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 2H, *J* = 8.6 Hz), 5.84 (dt, 1H, *J* = 15.7 Hz, *J* = 5.3 Hz), 5.68 (dd, 1H, *J* = 15.7 Hz, *J* = 7.5 Hz), 4.68 (s, 2H), 4.42 (d, 2H, *J* = 1.8 Hz), 4.10 (t, 2H, *J* = 5.3 Hz), 3.89 (dd, 1H, *J* = 7.4 Hz, *J* = 3.0 Hz) 3.79 (s, 3H), 3.78-3.73 (m, 1H), 3.72-3.65 (m, 3H), 3.65-3.60 (m, 1H), 3.60-3.55 (m, 1H), 3.55-3.50 (m, 2H), 3.43 (dd, 1H, *J* = 10.0 Hz, *J* = 5.5 Hz), 3.38 (dd, 1H, *J* = 10.2 Hz, *J* = 4.9 Hz), 3.37 (s, 3H), 2.72 (d, 1H, *J* = 4.6 Hz), 1.84-1.76 (m, 2H), 1.42-1.38 (m, 2H), 0.93 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 159.2, 133.4, 130.2, 129.2, 128.4, 113.7, 95.4, 82.0, 74.6, 74.0, 72.9, 72.3, 71.7, 66.9, 64.4, 62.9, 59.0, 55.3, 31.8, 24.9, 10.3; IR (neat) ν_{max} 3447, 2931, 2876, 1613, 1568, 1514, 1464, 1366, 1302, 1248, 1174, 1095, 1037, 980, 820, 741 cm^{-1}; LR-MS (ESI) *m/z* 465 ($M+Na^+$); HR-MS (ESI) calcd for $C_{23}H_{38}NaO_8$ ($M+Na^+$) 465.2464, found 465.2415.

(10*S*,12*S*,*E*)-12-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)propyl)-10-(hydroxymethyl)-2,5,7, 11-tetraoxapentadec-13-en-15-yl acetate (105). To a solution of diol **104** (1.13 g, 2.55 mmol) in CH_2Cl_2 (250 mL) was cooled to -10 ℃ and carefully added Ac_2O (0.253 mL, 2.68 mmol), DMAP (0.156 g, 1.28 mmol) and pyridine (0.227 mL, 2.81 mmol). After stirring for 1 h at the same temperature, the reaction mixture was quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (100 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:1) to afford alcohol (1.21 g, 98%) as a colorless oil: $[\alpha]_D^{25}$ +10.84 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.21 (d, 2H, *J* = 8.4 Hz), 6.85 (d, 2H, *J* = 8.5 Hz), 5.80-5.71 (m, 2H), 4.68 (s, 2H), 4.53 (d, 2H, *J* = 4.6 Hz), 4.41 (q, 2H, J_{AB} = 11.7 Hz), 3.90-3.88 (m, 1H), 3.78 (s, 3H), 3.77-3.72 (m, 1H),

3.72-3.68 (m, 1H), 3.66 (t, 2H, *J* = 4.4 Hz), 3.64-3.59 (m, 1H), 3.59-3.54 (m, 1H), 3.53 (t, 2H, *J* = 4.6 Hz), 3.42 (dd, 1H, *J* = 10.0 Hz, *J* = 5.2 Hz), 3.39 (d, 1H, *J* = 5.0 Hz), 3.37 (s, 3H), 2.03 (s, 3H), 1.88-1.74 (m, 2H), 1.41-1.35 (m, 2H), 0.93 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.7, 159.2, 131.5, 130.3, 129.3, 127.7, 113.8, 95.4, 82.1, 74.6, 74.6, 72.9, 72.4, 71.8, 67.0, 64.4, 64.3, 59.0, 55.3, 31.9, 24.8, 20.9, 10.4; IR (neat) ν_{max} 3471, 2929, 1739, 1613, 1514, 1463, 1366, 1302, 1247, 1205, 1174, 1096, 1036, 977, 821, 712 cm^{-1}; LR-MS (ESI) *m/z* 507 ($M+Na^+$); HR-MS (ESI) calcd for $C_{25}H_{40}NaO_9$ ($M+Na^+$) 507.2570, found 507.2585.

To a solution of alcohol (1.35 g, 2.79 mmol) in CH_2Cl_2 (30 mL) were added 2,6-lutidine (0.970 mL, 8.36 mmol) and TBSOTf (0.732 mL, 4.18 mmol) at 0 ℃. After stirring for 1 h, the reaction mixture was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (30 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:2) to afford silyl ether (1.67 g, 100%) as a colorless oil: $[\alpha]_D^{25}$ +10.86 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.21 (d, 2H, *J* = 8.5 Hz), 6.84 (d, 2H, *J* = 8.5 Hz), 5.71-5.65 (m, 2H), 4.67 (s, 2H), 4.51 (d, 2H, *J* = 4.6 Hz), 4.39 (q, 2H, J_{AB} = 11.6 Hz), 3.78 (s, 3H), 3.69 (t, 1H, *J* = 6.4 Hz), 3.67-3.62 (m, 3H), 3.62-3.56 (m, 3H), 3.52 (t, 2H, *J* = 4.6 Hz), 3.41 (dd, 1H, *J* = 10.0 Hz, *J* = 5.0 Hz), 3.36 (s, 3H), 3.34 (dd, 1H, *J* = 10.0 Hz, *J* = 5.4 Hz), 2.02 (s, 3H), 1.88-1.76 (m, 2H), 1.52-1.42 (m, 2H), 0.85 (s, 12H), 0.00 (d, 6H, *J* = 5.2 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.7, 159.1, 133.5, 130.5, 129.1, 127.0, 113.7, 95.5, 81.7, 75.8, 74.2, 72.8, 72.2, 71.8, 66.7, 64.5, 64.4, 59.0, 55.2, 32.1, 26.2, 25.9, 20.9, 18.2, 9.4, -4.2, -4.5; IR (neat) ν_{max} 2955, 2930, 2882, 1743, 1613, 1586, 1514, 1464, 1365, 1302, 1249, 1173, 1097, 1038, 976, 836, 777 cm^{-1}; LR-MS (FAB) *m/z* 597 ($M-H^+$); HR-MS (FAB) calcd for $C_{31}H_{53}O_9Si$ ($M-H^+$) 597.3459, found 597.3452.

To a solution of silyl ether (1.53 g, 2.55 mmol) in CH_2Cl_2 (25 mL) and pH 7 buffer solution (2.5 mL) was added DDQ (1.74 g, 7.66 mmol) in one portion at ambient temperature and

stirred for 2 h. The reaction mixture was filtered and quenched with a saturated $NaHCO_3$ solution (15 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:1) to afford alcohol **105** (1.16 g, 95%) as a colorless oil: $[\alpha]_D^{25}$ +37.22 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.72-5.66 (m, 2H), 4.68 (s, 2H), 4.59-4.52 (m, 2H), 3.71-3.64 (m, 3H), 3.64-3.55 (m, 5H), 3.53 (t, 2H, *J* = 4.7 Hz), 3.50-3.44 (m, 1H), 3.37 (s, 3H), 2.09 (t, 1H, *J* = 6.4 Hz), 2.04 (s, 3H), 1.85-1.80 (m, 1H), 1.80-1.72 (m, 1H), 1.51-1.41 (m, 2H), 0.86 (s, 12H), 0.02 (d, 6H, *J* = 2.7 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.7, 132.6, 128.3, 95.5, 81.1, 75.8, 75.2, 71.8, 66.9, 64.7, 64.2, 64.2, 59.0, 31.0, 26.4, 25.9, 20.9, 18.1, 9.5, -4.2, -4.5; IR (neat) ν_{max} 3481, 2954, 2930, 2883, 1743, 1463, 1366, 1247, 1114, 1097, 1050, 977, 837, 777, 677 cm^{-1}; LR-MS (FAB) *m/z* 479 ($M+H^+$); HR-MS (FAB) calcd for $C_{23}H_{47}O_8Si$ ($M+H^+$) 479.3040, found 479.3049.

(10*S*,12*S*,*E*)-12-((*R*)-1-((tert-butyldimethylsilyl)oxy)propyl)-10-(2-(phenylsulfonyl)acetyl)-2,5,7,11-tetraoxapentadec-13-en-15-yl acetate (103). To a solution of alcohol **105** (1.12 g, 2.34 mmol) in CH_2Cl_2 (20 mL) were added $NaHCO_3$ (0.590 g, 7.02 mmol) and Dess-Martin periodinane (1.98 g, 4.68 mmol) at ambient temperature, stirred for 1 h. The reaction mixture was quenched with a saturated $Na_2S_2O_3$ solution (20 mL) at 0 ℃ and extracted with CH_2Cl_2 (20 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of methyl phenyl sulfone (0.548 g, 3.51 mmol) in THF (20 mL) was added dropwise *n*-BuLi (1.36 mL, 2.5 M solution in *n*-hexane, 3.39 mmol) at 0 ℃ and stirred for 1h. The generated anion was carefully added to a solution of crude aldehyde in THF (10 mL) at -78 ℃ and subsequently warmed to 0 ℃. After stirring for 2 h, the reaction mixture was quenched with H_2O (15 mL) at the same temperature and extracted with EtOAc (20 mL × 2). The combined organic layer was washed with brine,

dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:1) to afford diastereomeric mixture of alcohol (1.07 g, 72%) as a colorless oil: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.92 (d, 2H, *J* = 8.0 Hz), 7.63 (t, 1H, *J* = 7.6 Hz), 7.55 (q, 2H, *J* = 7.6 Hz), 5.70-5.63 (m, 1H), 5.50 (dd, 0.7H, *J* = 15.8 Hz, *J* = 8.6 Hz), 5.41 (dd, 0.3H, *J* = 15.7 Hz, *J* = 8.8 Hz), 4.65 (s, 2H), 4.54-4.48 (m, 2H), 4.16-4.07 (m, 1H), 3.70-3,58 (m, 4H), 3.58-3.49 (m, 4H), 3.42 (q, 1H, *J* = 6.0 Hz), 3.37 (d, 3H, *J* = 4.1 Hz), 3.27 (d, 1H, *J* = 3.8 Hz), 3.16 (dd, 0.7H, *J* = 14.5 Hz, *J* = 10.0 Hz), 3.05 (d, 0.3H, *J* = 4.8 Hz), 2.06 (s, 0.8H), 2.03 (s, 2.2H), 1.96-1.81 (m, 1H), 1.79-1.61 (m, 1H), 1.44-1.33 (m, 2H), 0.83 (s, 12H), -0.01 (s, 3H), -0.05 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.7, 170.6, 140.1, 140.0, 133.7, 133.6, 131.5, 131.4, 129.5, 129.4, 129.2, 129.1, 128.1, 128.0, 95.5, 95.5, 82.2, 81.1, 76.2, 75.6, 75.5, 71.8, 67.9, 67.4, 67.1, 67.0, 64.2, 64.0, 63.9, 63.6, 59.3, 59.1, 59.0, 29.7, 29.5, 26.4, 26.3, 25.8, 20.9, 20.8, 18.1, 9.4, -4.2, -4.2, -4.4, -4.5; IR (neat) ν_{max} 3516, 2931, 2884, 2858, 1741, 1463, 1448, 1366, 1306, 1240, 1144, 1087, 1026, 979, 837, 780, 724, 689 cm^{-1}; LR-MS (ESI) *m/z* 655 (M+Na$^+$); HR-MS (ESI) calcd for $C_{30}H_{52}NaO_{10}SSi$ (M+Na$^+$) 655.2948, found 655.2949.

To a solution of diastereomeric mixture of alcohol (1.09 g, 1.72 mmol) in CH_2Cl_2 (15 mL) were added $NaHCO_3$ (0.434 g, 5.17 mmol) and Dess-Martin periodinane (1.46 g, 3.44 mmol) at ambient temperature. After stirring for 2 h, the reaction mixture was quenched with a saturated $Na_2S_2O_3$ solution (15 mL) at 0 ℃ and extracted with CH_2Cl_2 (15 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:3) to afford precursor **103** (1.09 g, 100%) as a colorless oil: $[\alpha]_D^{25}$ +7.64 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.91 (d, 2H, *J* = 8.0 Hz), 7.63 (t, 1H, *J* = 7.5 Hz), 7.54 (t, 2H, *J* = 7.7 Hz), 5.70 (dt, 1H, *J* = 15.8 Hz, *J* = 5.4 Hz), 5.63 (dd, 1H, *J* = 15.7 Hz, *J* = 7.9 Hz), 4.53 (s, 2H), 4.50 (t, 2H, *J* = 6.2 Hz), 4.38 (q, 2H, J_{AB} = 15.3 Hz), 4.00 (t, 1H, *J* = 5.8 Hz), 3.68-3.64 (m, 2H), 3.61-3.53 (m, 4H), 3.50 (t, 2H, *J* = 4.5 Hz), 3.36 (s, 3H), 2.00

(s, 3H), 2.00-1.94 (m, 1H), 1.94-1.86 (m, 1H), 1.51-1.42 (m, 2H), 0.85 (s, 12H), 0.02 (d, 6H, *J* = 6.9 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 200.1, 170.7, 139.7, 133.9, 130.7, 130.5, 129.0, 128.6, 95.3, 83.4, 80.5, 75.2, 71.8, 66.9, 63.4, 62.6, 61.8, 59.0, 31.2, 26.2, 25.8, 20.8, 18.1, 9.3, -4.2, -4.4; IR (neat) ν_{max} 2955, 2930, 2883, 1739, 1448, 1366, 1326, 1237, 1157, 1117, 1086, 1027, 837, 781, 753, 688 cm^{-1}; LR-MS (ESI) *m/z* 653 (M+Na$^+$); HR-MS (ESI) calcd for $C_{30}H_{50}NaO_{10}SSi$ (M+Na$^+$) 653.2792, found 653.2791.

(2*S*,8*S*,*Z*)-8-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)propyl)-2-(2-((2-methoxyethoxy)ethoxy)ethyl)-5,8-dihydro-2*H*-oxocin-3(4*H*)-one (106). To a solution of precursor **103** (852 mg, 1.35 mmol) in MeCN (45 mL) was added $Pd(dppe)_2$ (366 mg, 0.405 mmol) in one portion at ambient temperature. The reaction mixture was stirred at 45 ℃ for 1 h. The reaction mixture was concentrated *in vacuo* and directly filtered through a short column of silica gel (EtOAc:*n*-hexane = 1:2). The residue was used in the next step without further purification. To a solution of crude regioisomeric mixture in THF (20 mL) was added a solution of sodium in liquid ammonia at -78 ℃. After stirring 1 h, the reaction mixture was quenched with a saturated $NaHCO_3$ solution (30 mL) at the same temperature and extracted with EtOAc (30 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:3) to afford oxocene **106** (536 mg, 92%) as a colorless oil: $[\alpha]_D^{25}$ -104.42 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.80 (q, 1H, *J* = 11.1 Hz), 5.47 (dd, 1H, *J* = 11.4 Hz, *J* = 4.0 Hz), 4.67 (q, 2H, J_{AB} = 6.7 Hz), 3.90 (t, 1H, *J* = 4.8 Hz), 3.78 (dd, 1H, *J* = 9.1 Hz, *J* = 4.4 Hz), 3.71 (q, 1H, *J* = 5.5 Hz), 3.69-3.59 (m, 4H), 3.53 (t, 2H, *J* = 4.6 Hz), 3.46-3.39 (m, 1H), 3.38 (s, 3H), 2.86 (ddd, 1H, *J* = 14.7 Hz, *J* = 6.6 Hz, *J* = 3.2 Hz), 2.42-2.33 (m, 1H), 2.06-1.98 (m, 1H), 1.98-1.91 (m, 1H), 1.88-1.81 (m, 1H), 1.67-1.58 (m, 1H), 1.53-1.49 (m, 1H), 0.88 (t, 3H, *J* = 7.5 Hz), 0.86 (s, 9H), 0.03 (d, 6H, *J* = 3.1 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 215.2, 130.6, 129.3, 95.5, 85.0, 83.5, 75.9, 71.8, 66.8, 63.8, 59.0, 40.2, 33.6, 26.2, 25.9, 22.4, 18.1, 9.0, -4.3, -4.5; IR (neat) ν_{max} 2931, 2883, 1710, 1463,

154, 1118, 1046, 838, 740 cm^{-1}; LR-MS (FAB) *m/z* 431 ($M+H^+$); HR-MS (FAB) calcd for $C_{22}H_{43}O_6Si$ ($M+H^+$) 431.2829, found 431.2817.

For (2*S*,5*S*,6*S*)-6-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)propyl)-2-(2-((2-methoxyethoxy)-methoxy)ethyl)-5-vinyldihydro-2*H*-pyran-3(4*H*)-one (107). minor product **107** (16.2 mg, 3%) as a colorless oil: $[\alpha]_D^{25}$ -65.44 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.68 (ddd, 1H, *J* = 17.2 Hz, *J* =, 10.4 Hz, *J* = 7.8 Hz), 5.02 (dd, 2H, *J* = 13.4 Hz, *J* = 6.5 Hz), 4.67 (q, 2H, J_{AB} = 6.7 Hz), 3.81-3.76 (m, 2H), 3.69-3.62 (m, 4H), 3.54-3.52 (m, 2H), 3.39 (dd, 1H, *J* = 6.4 Hz, *J* = 2.5 Hz), 3.37 (s, 3H), 3.11 (quint, 1H, *J* = 5.2 Hz), 2.77 (dd, 1H, *J* = 14.8 Hz, *J* = 7.2 Hz), 2.28 (dd, 1H, *J* = 14.8 Hz, *J* = 4.7 Hz), 2.14-2.07 (m, 1H), 1.80-1.73 (m, 1H), 1.58-1.50 (m, 1H), 1.50-1.40 (m, 1H), 0.88 (s, 12H), 0.04 (d, 6H, *J* = 5.3 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 212.3, 140.0, 115.4, 95.4, 81.7, 79.3, 75.7, 71.8, 66.7, 63.6, 59.0, 41.3, 38.6, 30.7, 26.2, 25.9, 18.2, 10.2, -4.1, -4.6; IR (neat) ν_{max} 2957, 2930, 2883, 2858, 1732, 1472, 1414, 1385, 1254, 1118, 1046, 836, 796, 732 cm^{-1}; LR-MS (ESI) *m/z* 453 ($M+Na^+$); HR-MS (ESI) calcd for $C_{22}H_{42}NaO_6Si$ ($M+Na^+$) 453.2648, found 453.2637.

(2*S*,8*S*)-8-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)propyl)-2-(2-((2-methoxyethoxy)methox-y)ethyl)oxocan-3-one (108). To a solution of oxocene **106** (407 mg, 0.945 mmol) in EtOAc (15 mL) and MeOH (5mL) was carefully added 10 wt% Pd/C (407 mg). The reaction mixture was stirred for 30 min under a hydrogen atmosphere at ambient temperature, filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:3) to afford cyclic ether **108** (409 mg, 100%) as a colorless oil: $[\alpha]_D^{25}$ -53.08 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 4.65 (q, 2H, J_{AB} = 6.8 Hz), 3.72-3.68 (m, 1H), 3.68-3.62 (m, 3H), 3.62-3.56 (m, 2H), 3.53 (t, 2H, *J* = 4.6 Hz), 3.36 (s, 3H), 3.27 (dt, 1H, *J* = 7.3 Hz, *J* = 4.0 Hz), 2.95 (td, 1H, *J* = 11.0 Hz, *J* = 3.8 Hz), 2.05-2.02 (m, 1H), 1.94-1.86 (m, 2H), 1.79 (q, 2H, *J* = 6.6 Hz), 1.72-1.66 (m, 1H), 1.66-1.60 (m, 1H), 1.57-1.48 (m, 3H), 1.37-1.29 (m, 1H), 0.85 (s, 12H), 0.02 (d, 6H, *J* = 7.7 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 220.1, 95.5, 83.3, 82.5, 72.4,

71.8, 66.8, 63.5, 59.0, 37.4, 33.4, 29.1, 27.1, 26.0, 25.8, 22.5, 18.0, 7.8, -4.3, -4.7; IR (neat) ν_{max} 2930, 2883, 2859, 1714, 1463, 1384, 1349, 1254, 1102, 1047, 940, 837, 795, 666 cm^{-1}; LR-MS (FAB) *m/z* 433 ($M+H^+$); HR-MS (FAB) calcd for $C_{22}H_{45}O_6Si$ ($M+H^+$) 433.2985, found 433.2990.

(2*S*,8*S*,*Z*)-8-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)propyl)-2-(2-((2-methoxyethoxy)methoxy)ethyl)-7,8-dihydro-2*H*-oxocin-3(4*H*)-one (109). To a solution of cyclic ether **108** (252 mg, 0.582 mmol) in THF (15 mL) were added triethylamine (1.62 mL, 11.6 mmol), TMSCl (1.48 mL, 11.6 mmol) and LiHMDS (1.75 mL, 1.0 M solution in THF, 1.75 mmol) at -78 ℃. After stirring 1 h, the reaction mixture was quenched with H_2O (10 mL) at the same temperature and extracted with EtOAc (15 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was immediately used in the next step without further purification. To a solution of crude enol ether in MeCN (10 mL) was added $Pd(OAc)_2$ (654 mg, 2.91 mmol) in one portion at ambient temperature and stirred for 3 h. DBU (0.436 mL, 2.91 mmol) was added to the reaction mixture and stirred at 45 ℃ for 2 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 3:1) to afford ketone **109** (228 mg, 91%) as a colorless oil: $[\alpha]_D^{25}$ -205.70 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.82 (q, 1H, *J* = 9.0 Hz), 5.60 (q, 1H, *J* = 9.0 Hz), 4.66 (q, 2H, J_{AB} = 6.8 Hz), 3.99 (dd, 1H, *J* = 8.1 Hz, *J* = 4.2 Hz), 3.88 (ddd, 1H, *J* = 12.1 Hz, *J* = 7.9 Hz, *J* = 1.6 Hz), 3.72-3.59 (m, 5H), 3.53 (t, 2H, *J* = 4.6 Hz), 3.37 (s, 3H), 3.27 (td, 1H, *J* = 6.3 Hz, *J* = 1.7 Hz), 2.77 (dd, 1H, *J* = 12.1 Hz, *J* = 6.9 Hz), 2.44-2.36 (m, 1H), 2.26 (ddd, 1H, *J* = 14.8 Hz, *J* = 8.4 Hz, *J* = 1.6 Hz), 2.01-1.93 (m, 1H), 1.86-1.78 (m, 1H), 1.65-1.57 (m, 1H), 1.50-1.42 (m, 1H), 0.88 (s, 12H), 0.05 (d, 6H, *J* = 5.6 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 213.5, 129.7, 125.5, 95.4, 85.9, 82.6, 75.5, 71.8, 66.8, 63.7, 59.0, 40.9, 33.0, 28.6, 25.9, 26.4, 18.2, 9.0, -4.3, -4.4; IR (neat) ν_{max} 2956, 2930, 2883, 1718, 1462, 1387, 1317, 1254, 1118, 1045, 836, 780 cm^{-1}; LR-MS

(FAB) *m/z* 431 ($M+H^+$); HR-MS (FAB) calcd for $C_{22}H_{43}O_6Si$ ($M+H^+$) 431.2829, found 431.2835.

(2*S*,3*R*,8*S*,*Z*)-8-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)propyl)-2-(2-((2-methoxyethoxy)methoxy)ethyl)-3,4,7,8-tetrahydro-2*H*-oxocin-3-ol (110). To a solution of ketone **109** (143 mg, 0.332 mmol) in toluene (5 mL) was carefully added DIBAL-H (0.609 mL, 1.2 M solution in toluene, 0.731 mmol) at ambient temperature. After stirring for 30 min, the reaction mixture was quenched with Rochelle solution (5 mL) at 0 ℃ and extracted with EtOAc (10 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:1) to afford alcohol **110** (116 mg, 81%) as a colorless oil: $[\alpha]_D^{25}$ -15.86 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.87 (q, 1H, *J* = 8.0 Hz), 5.79 (q, 1H, *J* = 8.4 Hz), 4.69 (q, 2H, *J* = 6.8 Hz), 3.75-3.71 (m, 1H), 3.71-3.68 (m, 1H), 3.68-3.60 (m, 3H), 3.60-3.55 (m, 1H), 3.54 (t, 2H, *J* = 4.6 Hz), 3.40-3.39 (m, 1H), 3.37 (s, 3H), 3.21 (ddd, 1H, *J* = 7.5 Hz, *J* = 4.3 Hz, *J* = 1.5 Hz), 2.78 (td, 1H, *J* = 11.5 Hz, 3.1 Hz), 2.38-2.31 (m, 1H), 2.27-2.24 (m, 1H), 2.24-2.14 (m, 2H), 2.03-1.96 (m, 1H), 1.74-1.67 (m, 1H), 1.54-1.48 (m, 1H), 1.45-1.37 (m, 1H), 0.87 (s, 12H), 0.03 (d, 6H, *J* = 11.5 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 130.2, 128.3, 95.7, 83.7, 80.0, 76.5, 75.5, 71.8, 67.0, 65.0, 59.0, 34.4, 32.3, 28.5, 26.9, 26.0, 18.3, 9.5, -4.2, -4.5; IR (neat) ν_{max} 3481, 2929, 1252, 1087, 1045, 836 cm^{-1}; LR-MS (ESI) *m/z* 455 ($M+Na^+$); HR-MS (ESI) calcd for $C_{22}H_{44}NaO_6Si$ ($M+Na^+$) 455.2805, found 455.2794.

For (2*S*,3*S*,8*S*,*Z*)-8-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)propyl)-2-(2-((2-methoxyethoxy)methoxy)ethyl)-3,4,7,8-tetrahydro-2*H*-oxocin-3-ol (111). minor product **111** (24.4 mg, 17%) as a colorless oil: $[\alpha]_D^{25}$ +15.44 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.80 (q, 1H, *J* = 8.5 Hz), 5.71 (q, 1H, *J* = 8.4 Hz), 4.68 (q, 2H, *J* = 6.8 Hz), 3.73-3.69 (m, 1H), 3.69-3.64 (m, 3H), 3.64-3.59 (m, 2H), 3.58-3.51 (m, 3H), 3.37 (s, 3H), 3.24 (td, 1H, *J* = 6.4 Hz, *J* = 2.4 Hz), 2.52 (q, 1H, *J* = 11.0 Hz), 2.41-2.35 (m, 1H), 2.32-2.27 (m, 1H), 2.23 (ddd, 1H,

J = 14.0 Hz, *J* = 8.7 Hz, *J* = 2.3 Hz), 1.91 (d, 1H, *J* = 9.4 Hz), 1.89-1.83 (m, 1H), 1.79-1.72 (m, 1H), 1.62-1.56 (m, 1H), 1.50-1.41 (m, 1H), 0.89 (s, 9H), 0.87 (t, 3H, *J* = 7.5 Hz), 0.05 (d, 6H, *J* = 14.1 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 130.4, 128.6, 95.6, 82.5, 77.8, 75.6, 74.4, 71.8, 67.0, 64.6, 59.0, 33.2, 33.0, 28.5, 26.8, 26.0, 18.2, 9.1, -4.2, -4.4; IR (neat) ν_{max} 3482, 3018, 2955, 2882, 1463, 1389, 1253, 1173, 1089, 1051, 836, 795, 727 cm^{-1}; LR-MS (ESI) *m/z* 455 ($M+Na^+$); HR-MS (ESI) calcd for $C_{22}H_{44}NaO_6Si$ ($M+Na^+$) 455.2805, found 455.2788.

***tert*-butyl((*R*)-1-((2*S*,7*S*,8*S*,*Z*)-7-chloro-8-(2-((2-methoxyethoxy)methoxy)ethyl)-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl)propoxy)dimethylsilane (113).** To a solution of alcohol **110** (45.3 mg, 0.105 mmol) in CH_2Cl_2 (1 mL) were carefully added 2,6-lutidine (36.5 μL, 0.314 mmol) and McCl (14.0 μL, 0.157 mmol) at 0 °C. After stirring for 1 h at the same temperature, the reaction mixture was quenched with H_2O (1 mL) and extracted with CH_2Cl_2 (5 mL × 2). The combined organic layer was dried over $MgSO_4$, concentrated *in vacuo* and directly filtered through a short column of silica gel (EtOAc:*n*-hexane = 1:3). The residue was immediately used in the next step without further purification. To a solution of crude chloromethanesulfonate in DMF (2 mL) was added LiCl (31.1 mg, 0.733 mmol) in one portion at ambient temperature and stirred at 35 ℃ for 24 h. The reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (5 mL × 2). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:5) to afford chloride **113** (33.5 mg, 71%) as a colorless oil: $[\alpha]_D^{25}$ +8.94 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 800 MHz) δ 5.87 (q, 1H, *J* = 9.3 Hz), 5.64 (qd, 1H, *J* = 9.0 Hz, *J* = 1.8 Hz), 4.67 (q, 2H, J_{AB} = 6.7 Hz), 3.98-3.94 (m, 2H), 3.69-3.65 (m, 2H), 3.64-3.61 (m, 2H), 3.55 (dd, 1H, *J* = 8.6 Hz, *J* = 4.8 Hz), 3.53 (t, 2H, *J* = 4.6 Hz), 3.38 (s, 3H), 3.15 (dd, 1H, *J* = 9.2 Hz, *J* = 3.2 Hz), 2.94 (q, 1H, *J* = 11.7 Hz), 2.49-2.46 (m, 1H), 2.46-2.42 (m, 1H), 2.16 (ddd, 1H, *J* = 14.2 Hz, *J* = 8.6 Hz, *J* = 1.1 Hz), 1.98-1.93 (m, 1H), 1.75-1.71 (m, 1H), 1.56-1.52 (m, 1H), 1.44-1.38 (m,

1H), 0.88 (s, 12H), 0.11 (s, 3H), 0.04 (s, 3H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 131.9, 128.2, 95.5, 83.3, 76.6, 76.3, 71.8, 66.9, 66.0, 64.4, 591, 34.6, 34.5, 28.6, 27.3, 26.0, 18.3, 9.8, -4.1, -4.6; IR (neat) ν_{max} 2927, 2875, 1740, 1572, 1463, 1251, 1127, 1061, 902, 836, 798, 672 cm^{-1}; LR-MS (ESI) *m/z* 473 ($M+Na^+$); HR-MS (ESI) calcd for $C_{22}H_{43}Cl\ NaO_5Si$ ($M+Na^+$) 473.2466, found 473.2457.

2-((2*S*,3*S*,8*S*,*Z*)-8-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)propyl)-3-chloro-3,4,7,8-tetrahydro-2*H*-oxocin-2-yl)ethan-1-ol (115). To a solution of chloride **113** (21.6 mg, 47.9 μmol) in CH_2Cl_2 (0.5 mL) was carefully added $TiCl_4$ (71.8 μL, 1.0 M solution in CH_2Cl_2, 71.8 μmol) with bubbling of Ar gas at -78 ℃. After stirring for 30 min at the same temperature, the reaction mixture was warmed to 0 ℃ and stirred for additional 1 h. The reaction mixture was quenched with H_2O (2 mL) at the same temperature and extracted with CH_2Cl_2 (5 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:3) to afford alcohol **115** (16.0 mg, 92%) as a colorless oil: $[\alpha]_D^{25}$ +20.42 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.88 (q, 1H, *J* = 9.2 Hz), 5.66 (qd, 1H, *J* = 8.4 Hz, *J* = 1.3 Hz), 4.03-4.00 (m, 1H), 3.96 (ddd, 1H, *J* = 11.6 Hz, *J* = 5.0 Hz, *J* = 2.5 Hz), 3.76-3.69 (m, 2H), 3.66 (q, 1H, *J* = 4.5 Hz), 3.24 (dd, 1H, *J* = 9.7 Hz, *J* = 3.1 Hz), 2.94 (q, 1H, *J* = 11.2 Hz), 2.51-2.43 (m, 2H), 2.15 (dd, 1H, *J* = 14.2 Hz, *J* = 8.6 Hz), 2.03-1.95 (m, 1H), 1.71-1.64 (m, 1H), 1.60-1.54 (m, 1H), 1.48-1.41 (m, 2H), 0.89 (s, 12H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 131.9, 128.2, 83.6, 76.9, 76.5, 66.3, 59.5, 37.2, 34.5, 29.0, 27.0, 26.0, 18.3, 9.9, -4.1, -4.6; IR (neat) ν_{max} 3383, 2956, 2928, 2856, 1742, 1462, 1376, 1253, 1220, 1083, 1040, 835, 773, 687 cm^{-1}; LR-MS (ESI) *m/z* 363 ($M+H^+$); HR-MS (ESI) calcd for $C_{18}H_{36}ClO_3Si$ ($M+H^+$) 363.2122, found 363.2116.

***tert*-butyl((*R*)-1-((2*S*,7*S*,8*S*,*Z*)-7-chloro-8-((*E*)-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl)propoxy)dimethylsilane (116).** To a solution of alcohol **115** (11.0 mg, 30.3 μmol) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (38.6 mg,

90.9 μmol) at ambient temperature and stirred for 1 h. The reaction mixture was directly filtered through a short column of silica gel (EtOAc:*n*-hexane = 1:3). The residue was immediately used in the next step without further purification. To a solution of (3-trimethylsilyl-2-propynyl)triphenylphosphonium bromide (30.2 mg, 66.7 μmol) in THF (1 mL) was added dropwise *n*-BuLi (37.9 μL, 1.6 M in *n*-hexane, 60.6 μmol) at -78 ℃, warmed to 0 ℃ and stirred for 30 min. To a solution of crude aldehyde in THF (0.5 mL) was carefully added the ylide at -78 ℃ and stirred for 1 h. The reaction mixture was slowly warmed to 0 ℃ and stirred for additional 15 min. The reaction mixture was quenched with H_2O (1 mL) at the same temperature and extracted with EtOAc (5 mL × 2). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2:*n*-hexane = 1:3) to afford (*E*)-enyne **116** (11.4 mg, 83%) as a colorless oil: $[\alpha]_D^{25}$ +9.42 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.07 (dt, 1H, *J* = 15.9 Hz, *J* = 7.6 Hz), 5.87 (q, 1H, *J* = 9.3 Hz), 5.65-5.56 (m, 2H), 3.92 (ddd, 1H, *J* = 11.6 Hz, *J* = 5.0 Hz, *J* = 2.4 Hz), 3.76 (td, 1H, *J* = 6.7 Hz, *J* = 2.4 Hz), 3.66 (q, 1H, *J* = 5.0 Hz), 3.14 (dd, 1H, *J* = 9.7 H, *J* = 4.1 Hz), 2.93 (q, 1H, *J* = 11.2 Hz), 2.49-2.44 (m, 2H), 2.44-2.38 (m, 1H), 2.35-2.28 (m, 1H), 2.17 (dd, 1H, *J* = 14.0 Hz, *J* = 8.9 Hz), 1.58-1.54 (m, 1H), 1.45-1.38 (m, 1H), 0.89 (s, 12H), 0.15 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 141.2, 132.0, 128.1, 112.8, 103.6, 93.6, 83.1, 79.5, 76.2, 65.0, 38.0, 34.4, 28.8, 27.0, 26.0, 18.2, 9.4, -0.1, -4.2, -4.5; IR (neat) ν_{max} 2926, 2858, 1739, 1459, 1355, 1252, 1129, 1059, 896, 801, 656 cm^{-1}; LR-MS (ESI) *m/z* 455 ($M+H^+$); HR-MS (ESI) calcd for $C_{24}H_{44}ClO_2Si_2$ ($M+H^+$) 455.2568, found 455.2560.

(*R*)-1-((2*S*,7*S*,8*S*,*Z*)-7-chloro-8-((*E*)-pent-2-en-4-yn-1-yl)-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl)propan-1-ol (117). To a solution of (*E*)-enyne **116** (6.8 mg, 14.9 μmol) in THF (0.5 mL) was added TBAF (74.7 μL, 1.0 M solution in THF, 74.7 μmol) at 0 °C. After the stirring at ambient temperature for 24 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane =

1:3) to afford alcohol **117** (3.9 mg, 98%) as a white solid: $[\alpha]_D^{25}$ -2.82 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.14 (dt, 1H, *J* = 15.9 Hz, *J* = 7.6 Hz), 5.89 (q, 1H, *J* = 9.1 Hz), 5.68-5.64 (m, 1H), 5.58 (dd, 1H, *J* = 15.9 Hz, *J* = 1.9 Hz), 3.94 (ddd, 1H, *J* = 11.6 Hz, *J* = 5.0 Hz, *J* = 2.5 Hz), 3.83 (td, 1H, *J* = 6.9 Hz, *J* = 2.4 Hz), 3.58-3.52 (m, 1H), 3.26 (dd, 1H, *J* = 9.6 Hz, *J* = 3.6 Hz), 2.91 (q, 1H, *J* = 11.1 Hz), 2.81 (d, 1H, *J* = 2.0 Hz), 2.55-2.44 (m, 3H), 2.36-2.30 (m, 1H), 2.11 (ddd, 1H, *J* = 14.2 Hz, *J* = 8.5 Hz, *J* = 1.1 Hz), 1.98 (d, 1H, *J* = 5.7 Hz), 1.51-1.41 (m, 2H), 0.97 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 141.6, 131.4, 128.3, 112.0, 83.8, 81.8, 79.2, 76.7, 75.9, 64.8, 38.0, 34.3, 28.8, 25.3, 10.3; IR (neat) ν_{max} 3763, 3312, 2921, 2851, 1747, 1633, 1532, 1261, 1022, 800, 725, 638 cm^{-1}; LR-MS (ESI) *m/z* 291 (M+Na$^+$); HR-MS (ESI) calcd for $C_{15}H_{21}ClNaO_2$ (M+Na$^+$) 291.1128, found 291.1129.

(+)-(3*E*)-Pinnatifidenyne (6). To a solution of alcohol **117** (1.8 mg, 6.70 μmol) in toluene (0.3 mL) were added CBr_4 (3.3 mg, 10.0 μmol) and P(*n*-Oct)$_3$ (3.3 μL, 16.7 μmol) at ambient temperature. The reaction mixture was stirred at 70 ℃ for 6 h, cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:*n*-hexane = 1:5) to afford (+)-(3*E*)-Pinnatifidenyne (**6**) (2.1 mg, 93%) as a white solid: $[\alpha]_D^{25}$ +8.10 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.11 (dt, 1H, *J* = 15.9 Hz, *J* = 7.6 Hz), 5.89 (q, 1H, *J* = 9.0 Hz), 5.67 (ddd, 1H, *J* = 10.1 Hz, *J* = 6.6 Hz, *J* = 1.6 Hz), 5.57 (dd, 1H, *J* = 15.9 Hz, *J* = 1.3 Hz), 3.96-3.90 (m, 2H), 3.83 (td, 1H, *J* = 7.0 Hz, *J* = 2.4 Hz), 3.45 (dd, 1H, *J* = 10.2 Hz, *J* = 3.5 Hz), 2.94 (q, 1H, *J* = 11.4 Hz), 2.82 (d, 1H, *J* = 2.1 Hz), 2.64-2.56 (m, 1H), 2.55-2.49 (m, 2H), 2.39 (q, 1H, *J* = 7.1 Hz), 2.33 (dd, 1H, *J* = 14.1 Hz, *J* = 8.5 Hz), 2.01 (dqd, 1H, *J* = 14.4 Hz, *J* = 7.3 Hz, *J* = 3.6 Hz), 1.81-1.75 (m, 1H), 1.06 (t, 3H, *J* = 7.3 Hz); ^{13}C-NMR ($CDCl_3$, 200 MHz) δ 141.3, 130.9, 128.8, 112.1, 83.2, 81.9, 79.5, 76.8, 64.5, 61.1, 37.7, 34.3, 30.4, 27.3, 12.8; IR (neat) ν_{max} 3325, 2925, 1466, 1094, 1024, 798 cm^{-1}; LR-MS (ESI) *m/z* 353 (M+Na$^+$); HR-MS (ESI) calcd for $C_{15}H_{20}BrClNaO$ (M+Na$^+$) 353.0284, found 353.0278.

V. References

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VI. Appendix

^{1}H-NMR and ^{13}C-NMR data of (+)-(3*E*)-Pinnatifidenyne

Table 1. ^{1}H-NMR ($CDCl_3$, 500 MHz) data of (+)-(3*E*)-Pinnatifidenyne

Proton at Carbon No.	^{1}H-NMR	
	Natural (+)-(3*E*)-Pinnatifidenyne (260 MHz, $CDCl_3$)	Synthetic (+)-(3*E*)-Pinnatifidenyne (500 MHz, $CDCl_3$)
1	2.83 (d, *J* = 1.6 Hz)	2.82 (d, *J* = 2.1 Hz)
3	5.59 (dd, *J* = 15.7, 1.6 Hz)	5.57 (dd, *J* = 15.9, 1.3 Hz)
4	6.14 (dt, *J* = 15.7, 7.7 Hz)	6.11 (dt, *J* = 15.9, 7.6 Hz)
5	2.40 (dt, *J* = 14.1, 7.7 Hz) 2.35 (ddd, *J* = 14.1, 7.8, 7.7 Hz)	2.39 (q, *J* = 7.1 Hz) 2.33 (dd, *J* = 14.1, 8.5 Hz)
6	3.82 (ddd, *J* = 7.8, 7.7, 2.3 Hz)	3.83 (td, , *J* = 7.0, 2.4 Hz)
7	3.93 (ddd, *J* = 10.6, 3.0, 2.3 Hz)	3.96-3.90 (m)
8	2.95 (ddd, *J* = 12.3, 10.6, 7.0 Hz) 2.53 (ddd, *J* = 12.3, 3.0, 1.2 Hz)	2.94 (q, *J* = 11.4 Hz) 2.55-2.49 (m)
9	5.69 (ddd, *J* = 10.5, 7.0, 1.2 Hz)	5.67 (ddd, *J* = 10.1, 6.6, 1.6 Hz)
10	5.91 (ddd, *J* = 10.5, 7.9, 0.1 Hz)	5.89 (q, *J* = 9.0 Hz)
11	2.63 (ddd, *J* = 14.2, 10.5, 0.1 Hz) 2.35 (ddd, *J* = 14.2, 7.9, 3.1 Hz)	2.64-2.56 (m) 2.33 (dd, *J* = 14.1, 8.5 Hz)
12	3.46 (ddd, *J* = 10.5, 4.3, 3.1 Hz)	3.45 (dd, *J* = 10.2, 3.5 Hz)
13	3.96 (ddd, *J* = 11.5, 4.3, 3.6 Hz)	3.96-3.90 (m)
14	2.01 (dqd, *J* = 14.5, 7.2, 3.6 Hz) 1.80 (ddq, *J* = 14.5, 11.5, 7.2 Hz)	2.01 (dqd, *J* = 14.4, 7.3, 3.6 Hz) 1.81-1.75 (m)
15	1.07 (t, *J* = 7.2 Hz)	1.06 (t, *J* = 7.3 Hz)

Table 2. ^{13}C-NMR ($CDCl_3$, 200 MHz) data of (+)-(3*E*)-Pinnatifidenyne

Carbon No.	Natural[1] (+)-(3*E*)-Pinnatifidenyne (20 MHz, $CDCl_3$)	Δ δ (Nat.-Syn.)	Synthetic (+)-(3*E*)-Pinnatifidenyne (200 MHz, $CDCl_3$)
1	76.8	0	76.8[2,3]
2	Not observed (81.9)[3]	0	81.9
3	112.1	0	112.1
4	141.3	0	141.3
5	37.7	0	37.7
6	79.5	0	79.5
7	64.5	0	64.5
8	34.3	0	34.3
9	128.8	0	128.8
10	130.9	0	130.9
11	30.5	-0.1	30.4
12	83.3	-0.1	83.2
13	61.0	+0.1	61.1
14	27.4	-0.1	27.3
15	12.8	0	12.8

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(2) Carbon (1) of synthetic product was overlapped with the peak of $CDCl_3$.

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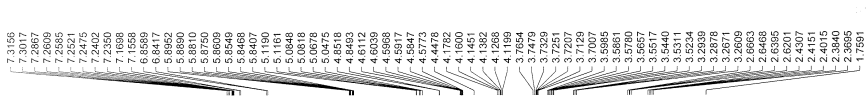
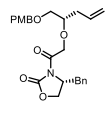
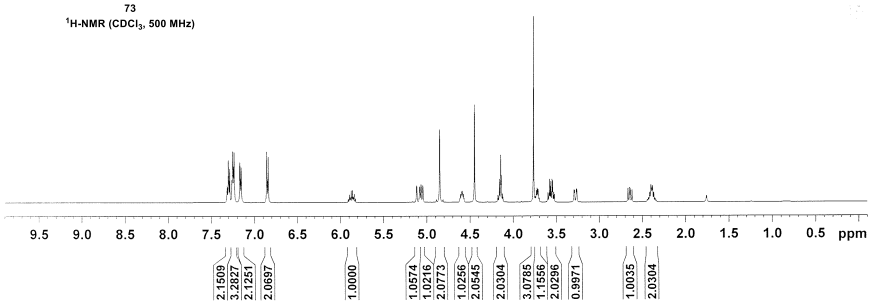
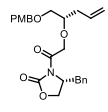




73

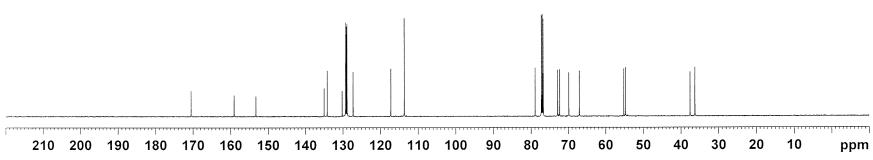
^{1}H-NMR ($CDCl_3$, 500 MHz)

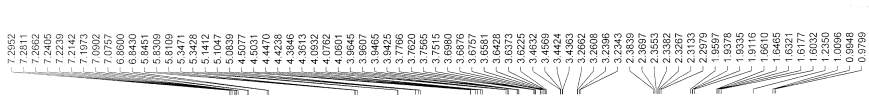


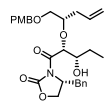


73

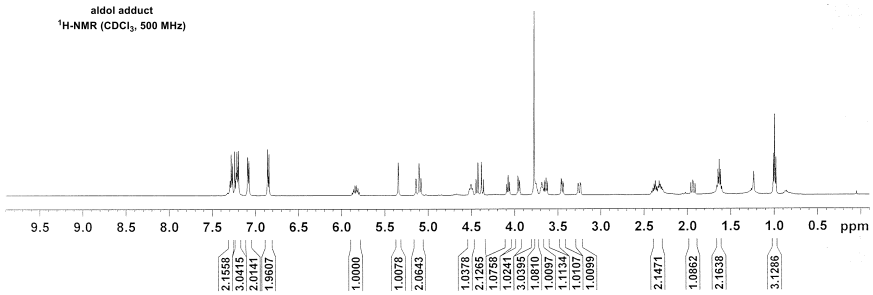
^{13}C-NMR ($CDCl_3$, 125 MHz)

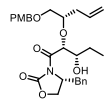






aldol adduct
^{1}H-NMR ($CDCl_3$, 500 MHz)





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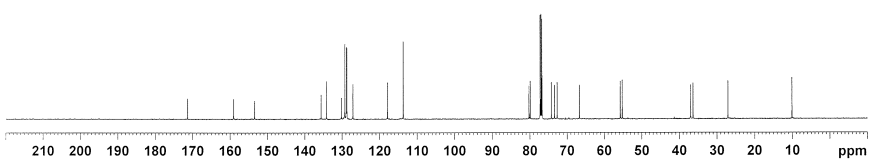

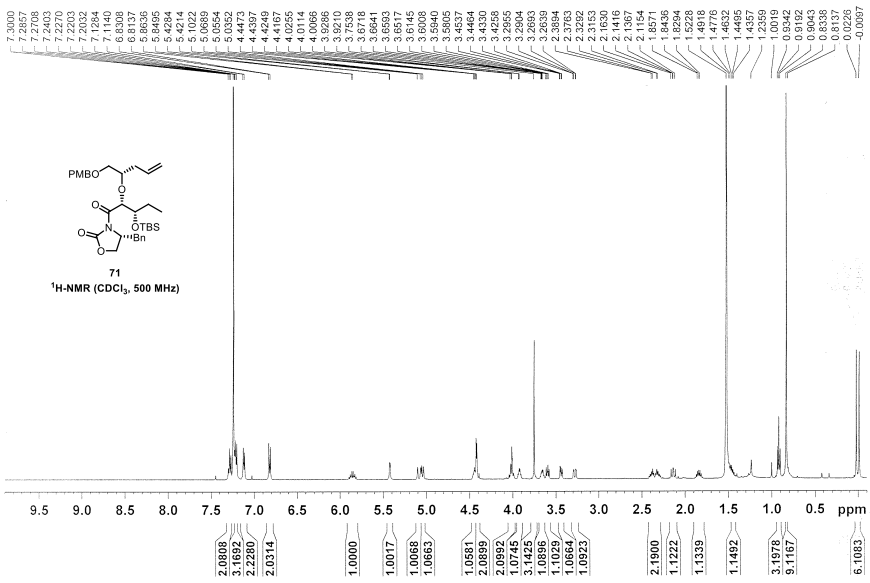
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OTBS
Bn
71
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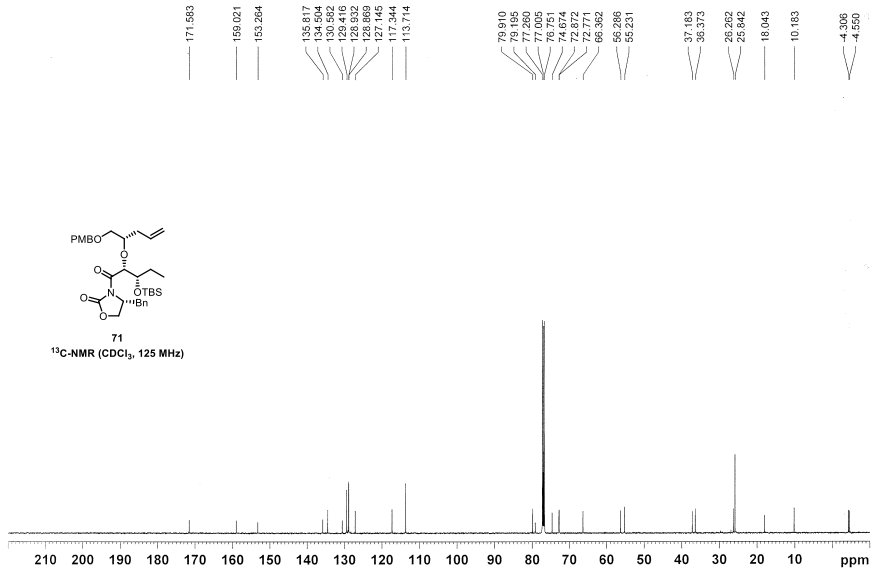
ppm


PMBO
OTBS
Bn
71
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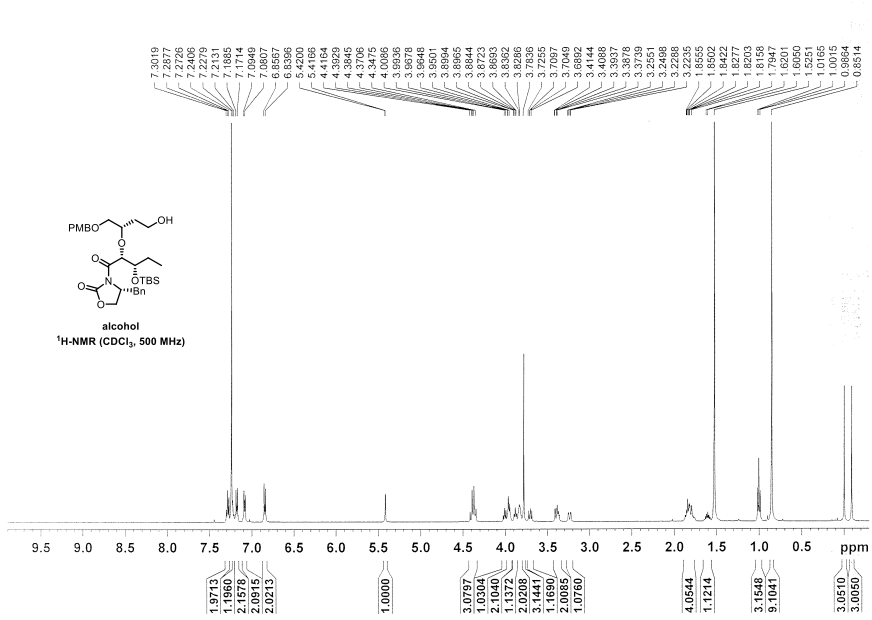
ppm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7.2496
7.2279
7.2131
7.1885
7.1714
7.0949
7.0807
6.8857
6.8696
5.4200
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4.3706
4.3575
4.0086
3.9936
3.9678
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3.9501
3.8994
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3.8362
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1.8203
1.8158
1.7947
1.6201
1.6050
1.5251
1.0155
1.0015
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0.8514
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.9713
1.1960
2.1578
2.0915
2.0213
1.0000
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1.0304
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1.1372
2.0208
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1.1690
2.0085
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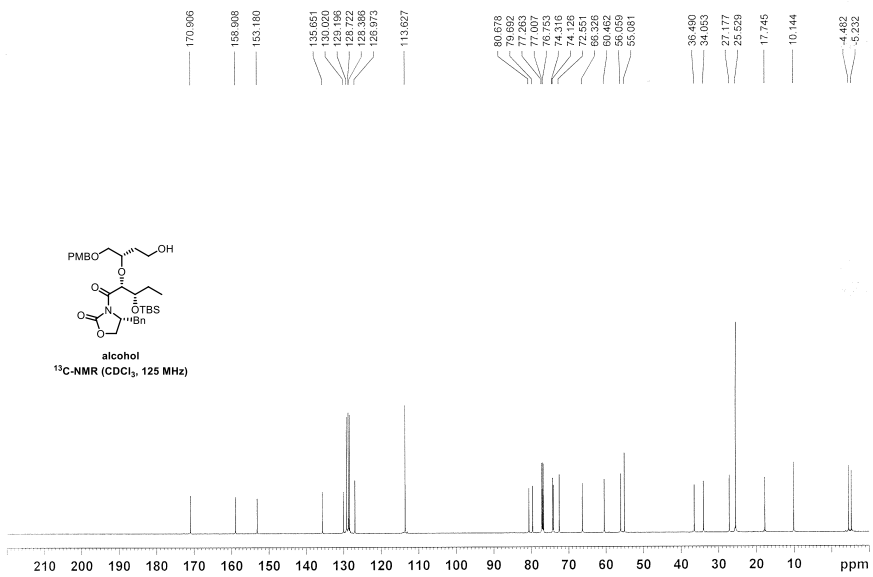
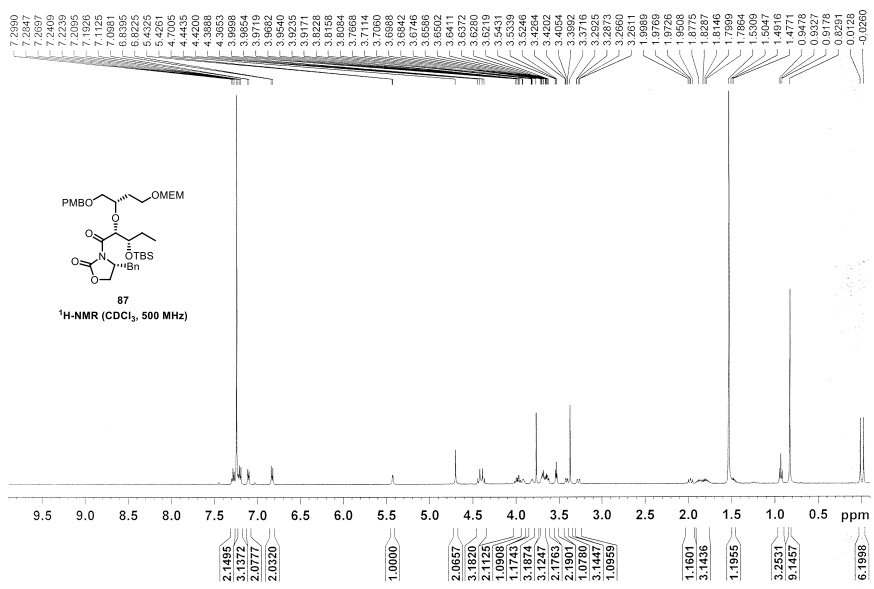
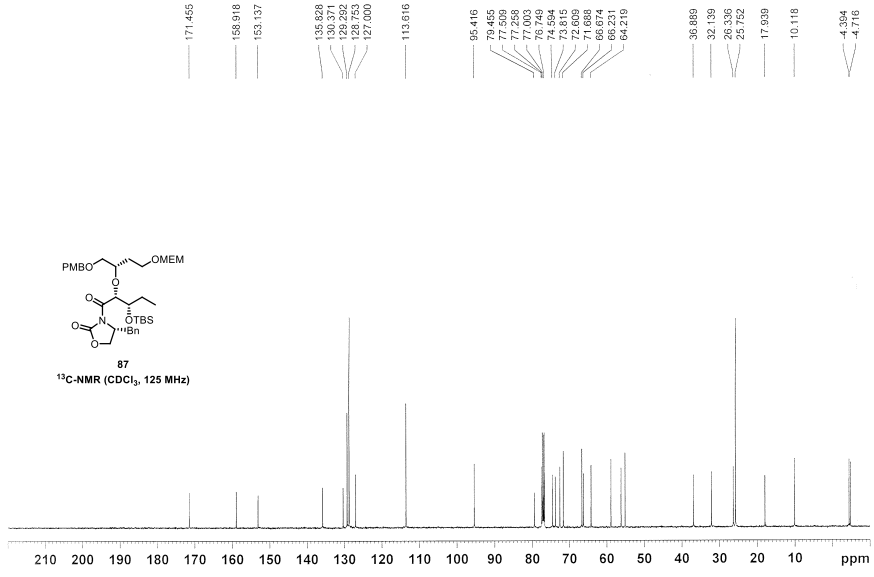
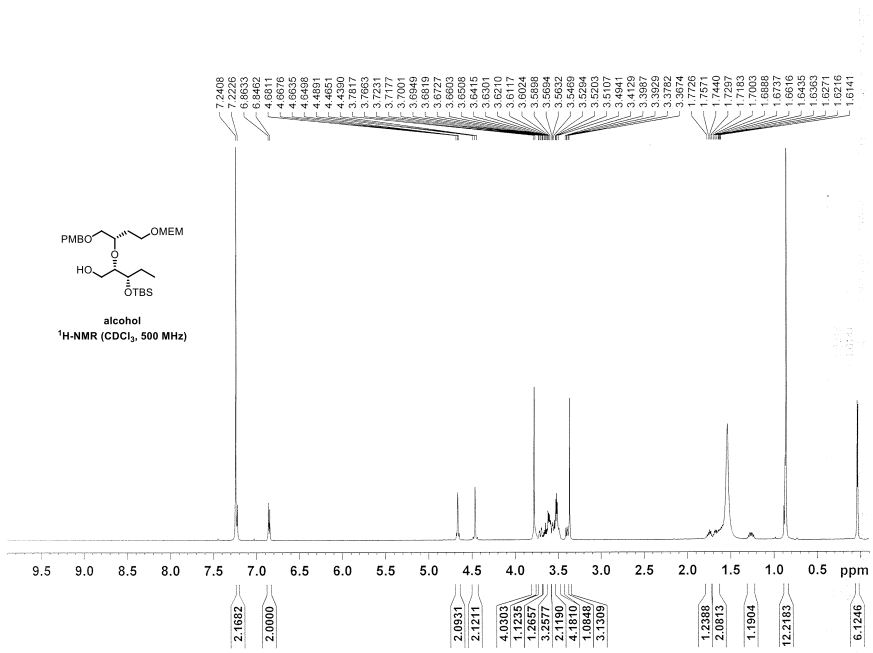
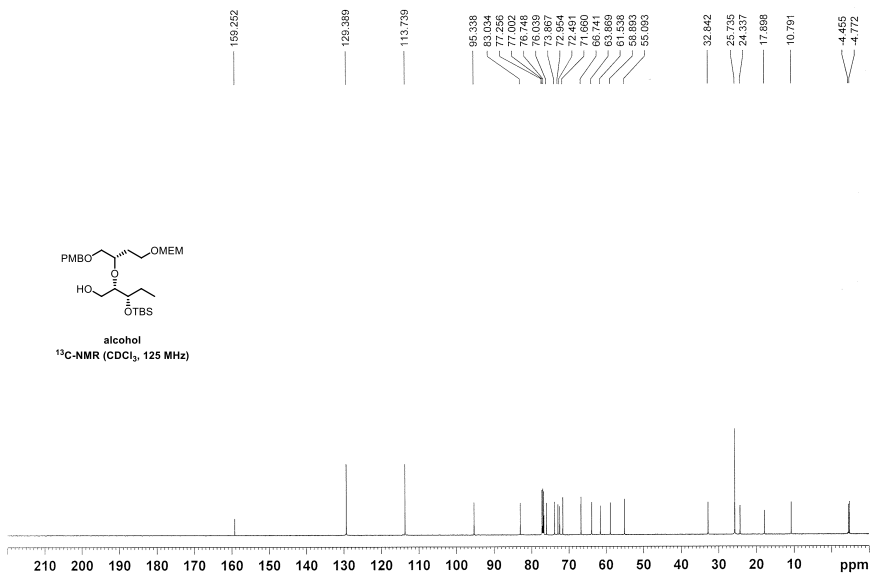
4.0544
1.1214
3.1548
9.1041
3.0510
3.0050

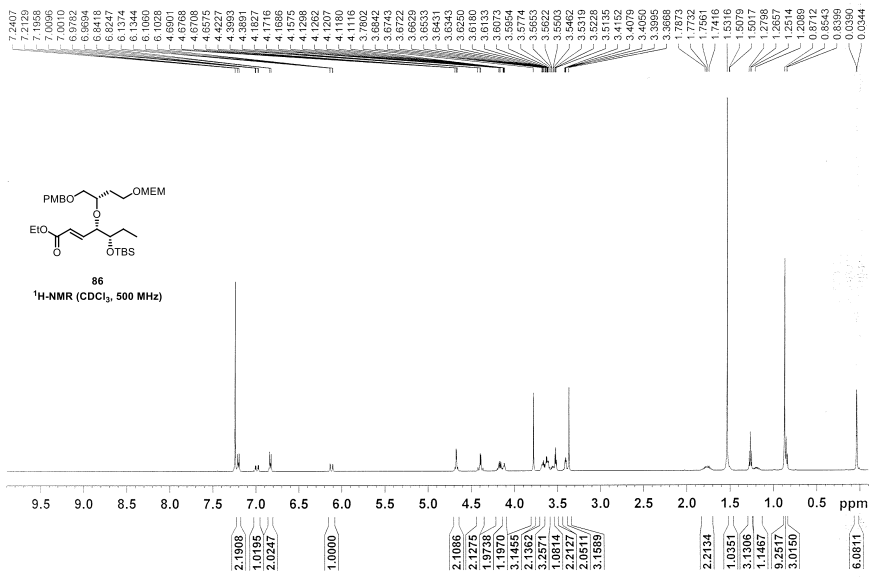

170.906
158.908
153.180
135.651
130.020
129.196
128.722
128.386
126.973
113.627
80.678
79.692
77.283
77.007
76.753
74.316
74.126
72.451
66.326
60.462
56.059
55.081
36.490
34.053
27.177
25.529
17.745
10.144
-4.482
-5.232
PMBO
OH
O
N
O
O
OTBS
Bn
alcohol
^{13}C-NMR ($CDCl_3$, 125 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

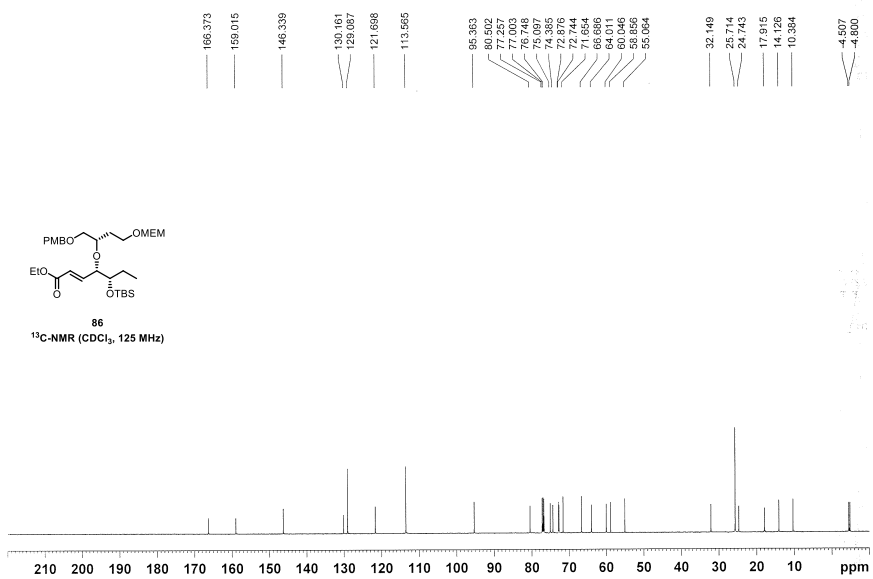

PMBO
OMEM
OTBS
Bn
87
^{1}H-NMR (CDCl$_3$, 500 MHz)
ppm

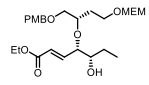

PMBO
OMEM
OTBS
Bn
87
^{13}C-NMR (CDCl$_3$, 125 MHz)
ppm


PMBO
OMEM
HO
OTBS
alcohol
^{1}H-NMR (CDCl$_3$, 500 MHz)
7.2408
7.2226
6.8633
6.8462
4.6811
4.6676
4.6635
4.6498
4.4661
4.4651
4.4390
3.7817
3.7663
3.7231
3.7077
3.7000
3.6949
3.6819
3.6727
3.6603
3.6508
3.6415
3.6301
3.6210
3.6117
3.6024
3.5898
3.5694
3.5632
3.5469
3.5284
3.5203
3.5107
3.4941
3.4129
3.3987
3.3929
3.3732
3.3074
1.7726
1.7571
1.7440
1.7297
1.7183
1.7093
1.6888
1.6737
1.6616
1.6435
1.6363
1.6271
1.6216
1.6141
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.1682
2.0000
2.0931
2.1211
4.0303
1.1235
1.2657
3.2577
2.1190
4.1810
1.0948
3.1309
1.2388
2.0813
1.1904
12.2183
6.1246

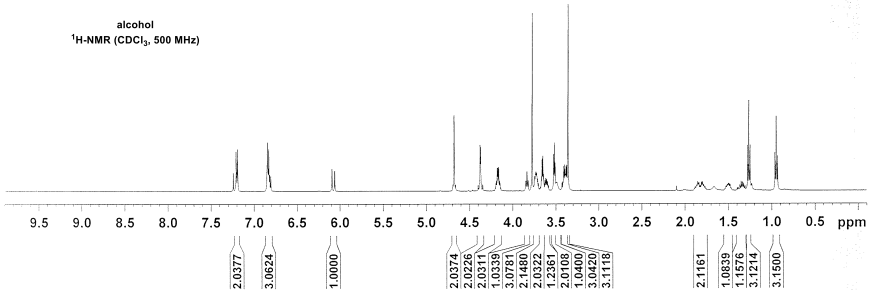

PMBO
OMEM
HO
OTBS
alcohol
^{13}C-NMR (CDCl$_3$, 125 MHz)
159.252
129.389
113.739
95.338
83.034
77.366
77.002
76.748
76.039
73.867
72.954
72.491
71.660
66.741
63.869
61.538
58.893
55.093
32.842
25.735
24.337
17.898
10.791
-4.455
-4.772
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

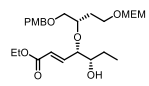

PMBO
OMEM
EtO
O
OTBS
86
^{1}H-NMR (CDCl$_3$, 500 MHz)
ppm


PMBO
OMEM
EtO
O
OTBS
86
^{13}C-NMR (CDCl$_3$, 125 MHz)
ppm

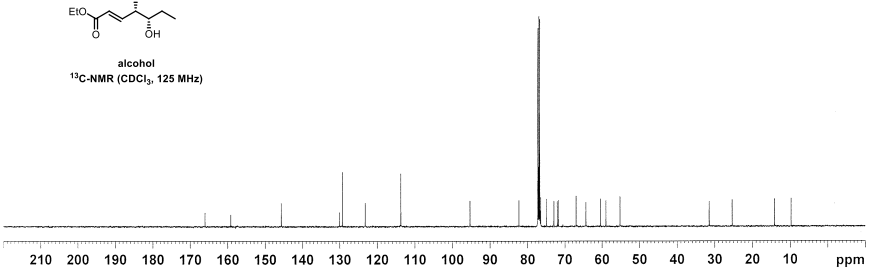


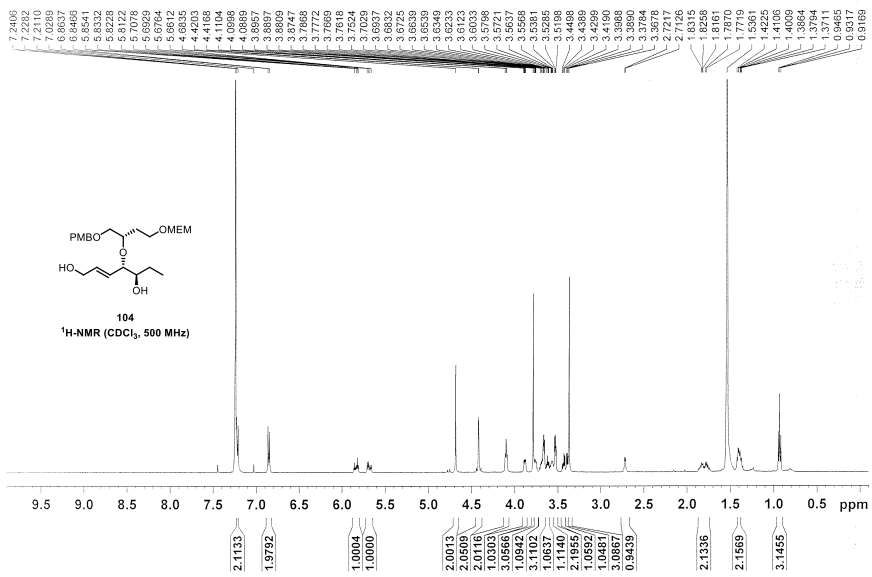
alcohol
^{1}H-NMR ($CDCl_3$, 500 MHz)

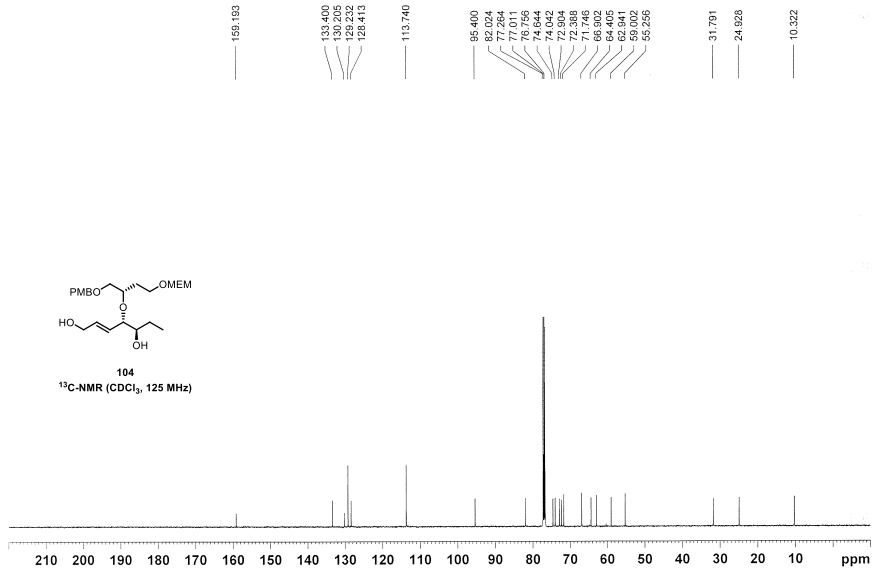


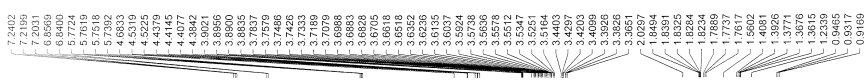


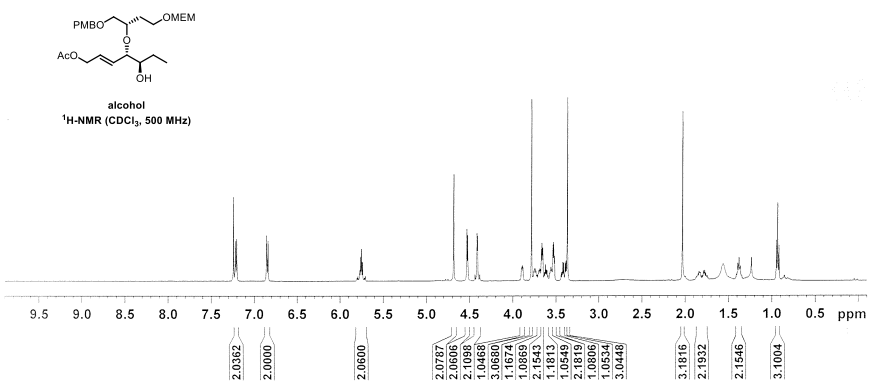
alcohol
^{13}C-NMR ($CDCl_3$, 125 MHz)

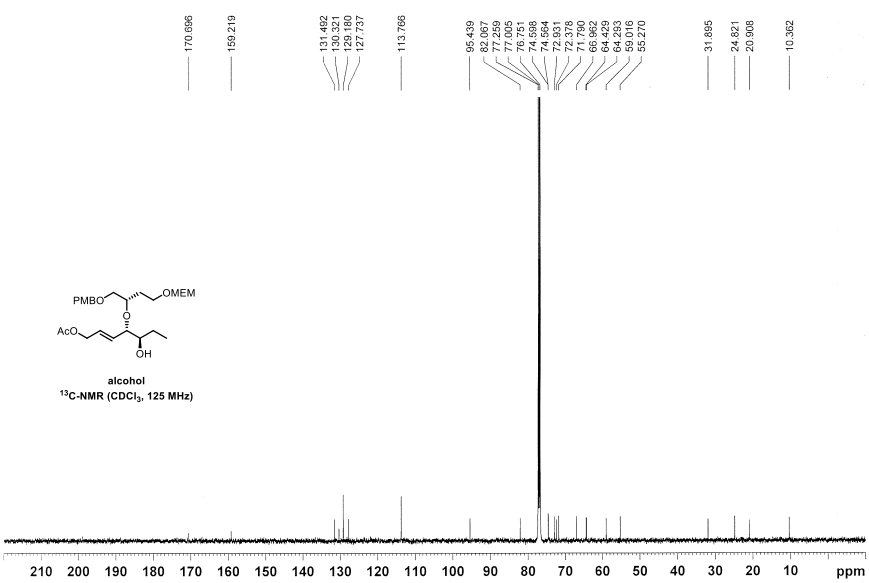


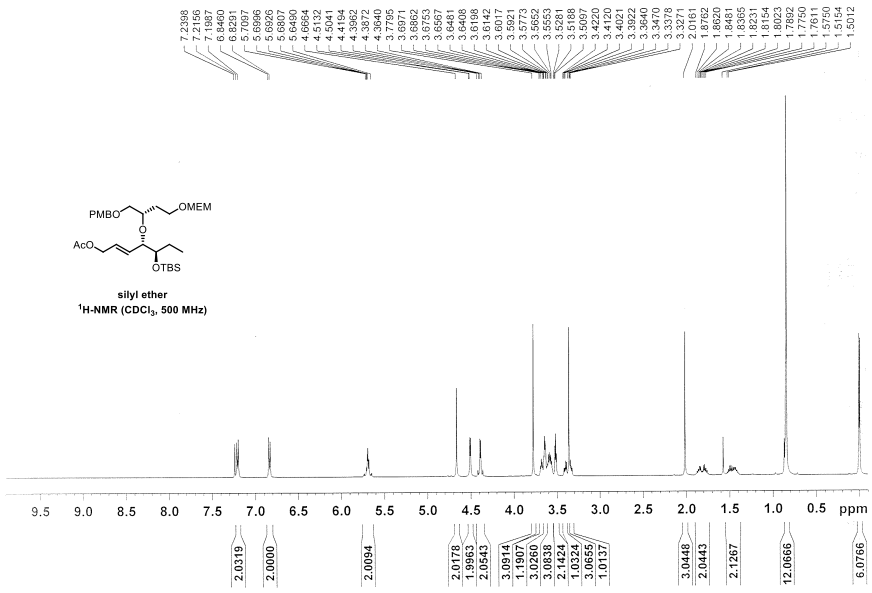

PMBO
OMEM
HO
OH
104
^{1}H-NMR ($CDCl_3$, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.1133 1.9792 1.0004 1.0000 2.0013 2.0509 2.0116 1.0303 3.0566 1.0942 3.1102 1.0637 1.1140 2.1955 1.0592 1.0481 3.0867 0.9439 2.1336 2.1569 3.1455

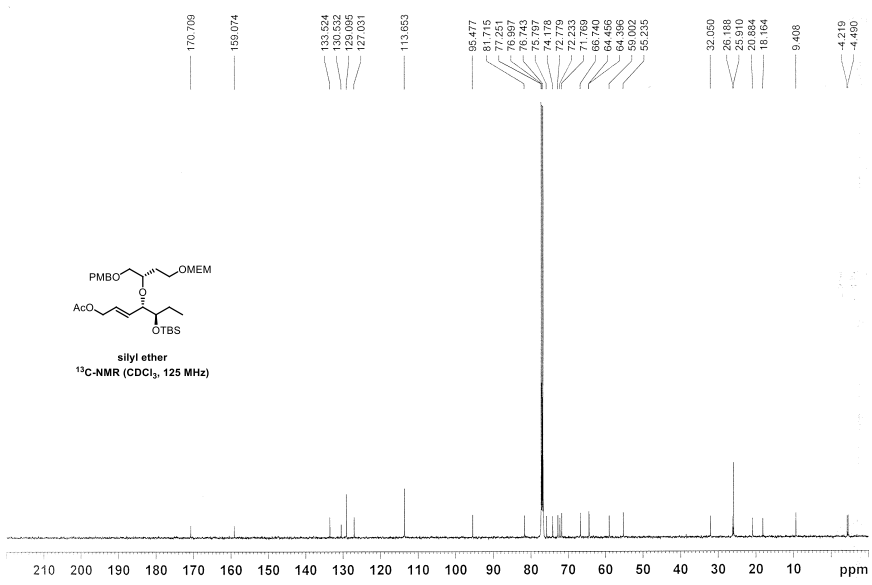

159.193
133.400
130.205
129.232
128.413
113.740
95.400
82.024
77.284
77.011
76.756
74.644
74.042
72.904
72.388
71.746
69.602
64.405
62.941
59.002
55.256
31.791
24.928
10.322
PMBO
OMEM
HO
OH
104
^{13}C-NMR ($CDCl_3$, 125 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

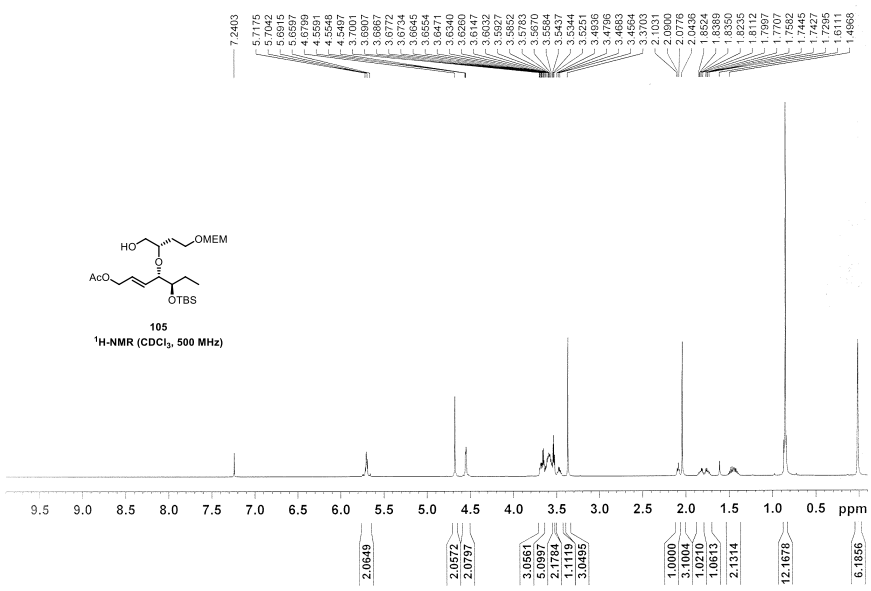


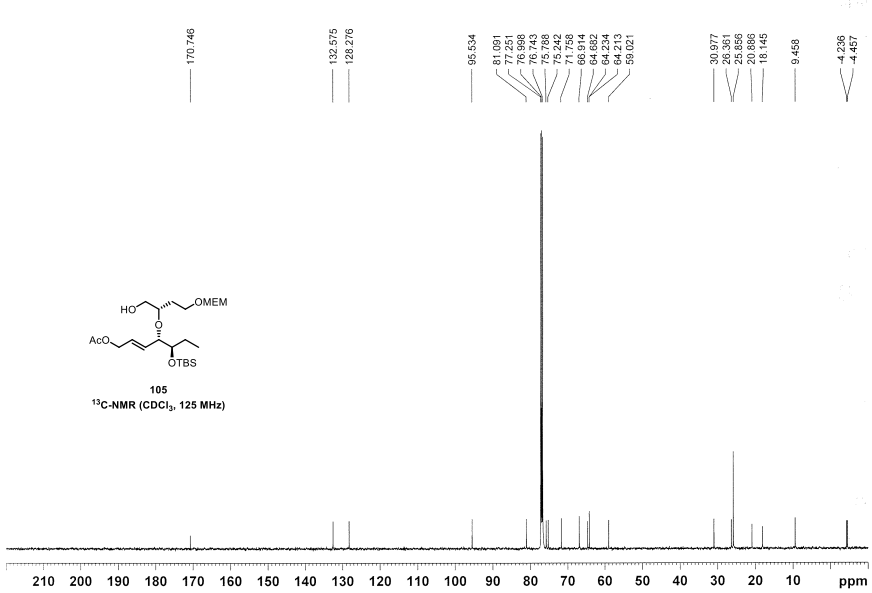

PMBO
OMEM
AcO
O
OH
alcohol
^{1}H-NMR ($CDCl_3$, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.0362
2.0000
2.0600
2.0787
2.0606
2.1098
1.0468
3.0680
1.1674
1.0869
2.1543
1.1813
1.0549
2.1819
1.0806
1.0534
3.0448
3.1816
2.1932
2.1546
3.1004

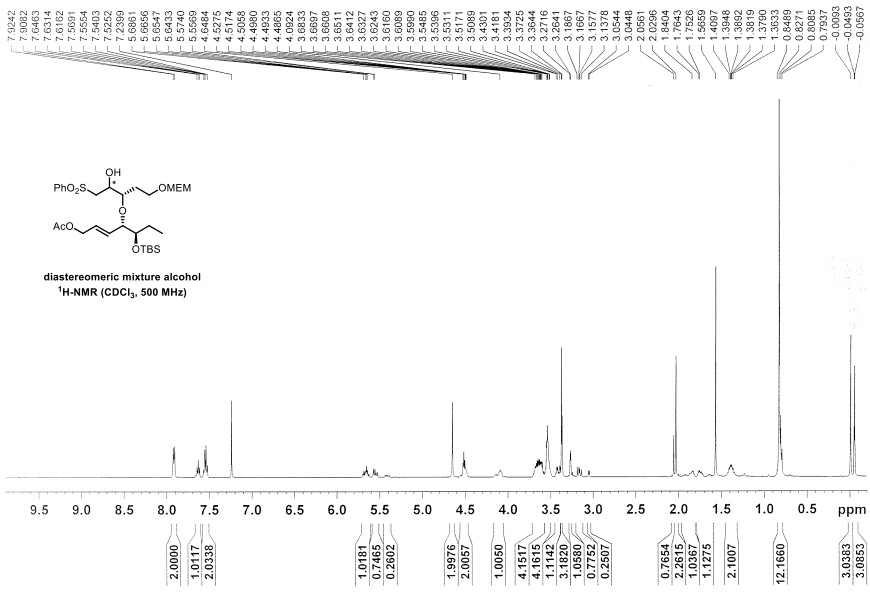

PMBO
OMEM
AcO
O
OH
alcohol
^{13}C-NMR ($CDCl_3$, 125 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

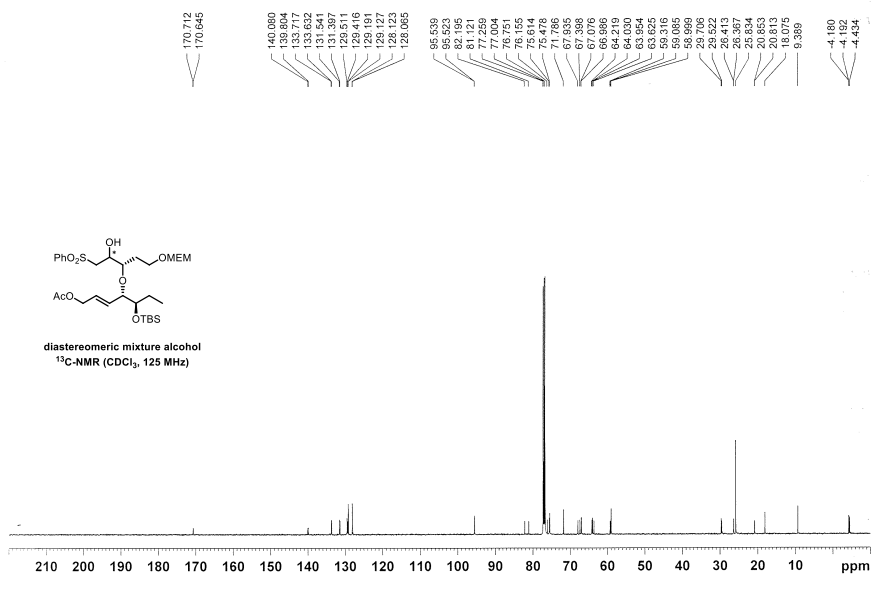

PMBO
OMEM
AcO
OTBS
silyl ether
^{1}H-NMR (CDCl$_3$, 500 MHz)
ppm

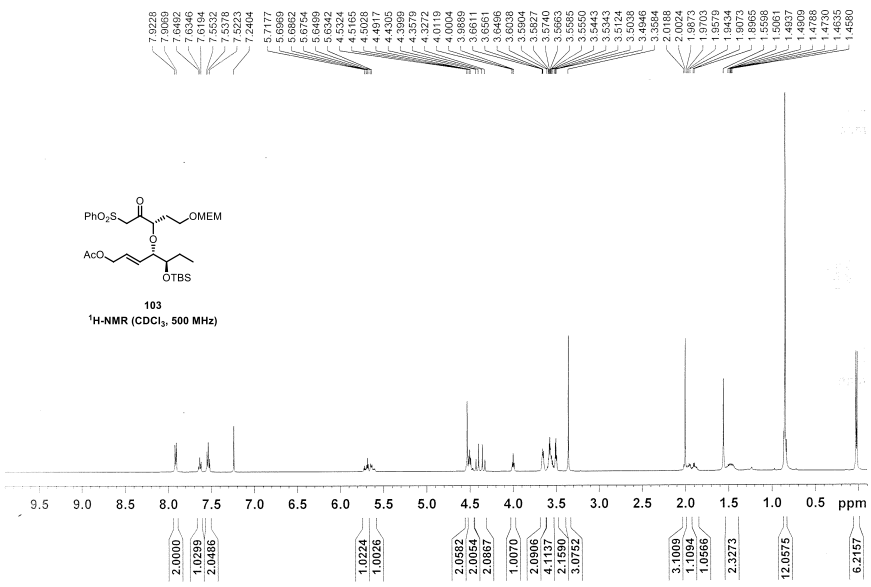

PMBO
OMEM
AcO
OTBS
silyl ether
^{13}C-NMR (CDCl$_3$, 125 MHz)
ppm

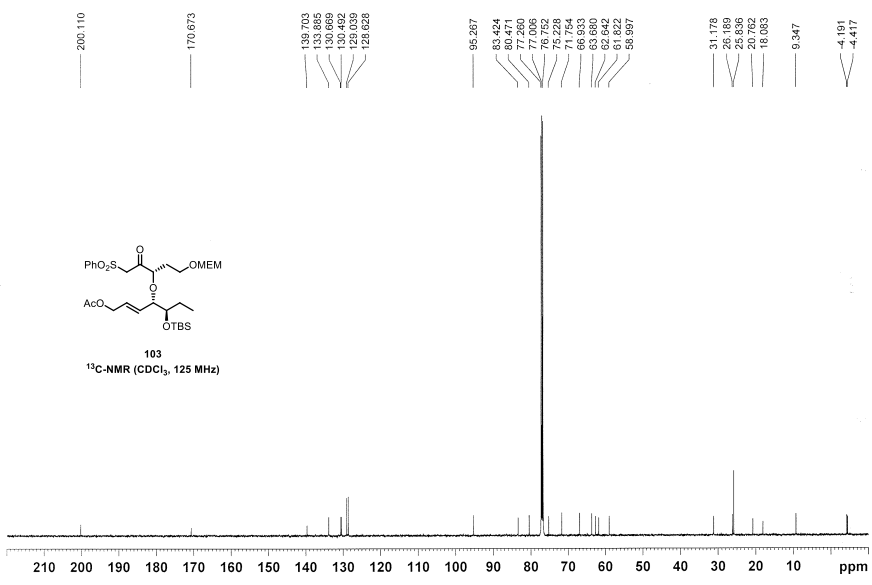

7.2403
5.7175
5.7042
5.6915
5.6597
4.6789
4.5991
4.5548
4.5497
3.7001
3.6907
3.6867
3.6772
3.6734
3.6645
3.6554
3.6471
3.6340
3.6260
3.6147
3.6052
3.5927
3.5852
3.5783
3.5670
3.5584
3.5437
3.5344
3.5251
3.4936
3.4796
3.4683
3.4564
3.3703
2.1031
2.0990
2.0778
2.0436
1.8524
1.8389
1.8350
1.8235
1.8012
1.7907
1.7707
1.7582
1.7445
1.7427
1.7295
1.6111
1.4868
HO
OMEM
AcO
OTBS
105
1H-NMR (CDCl3, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.0649
2.0572
2.0797
3.0561
5.0997
2.1784
1.1119
3.0495
1.0000
3.1004
1.0210
1.0613
2.1314
12.1678
6.1856

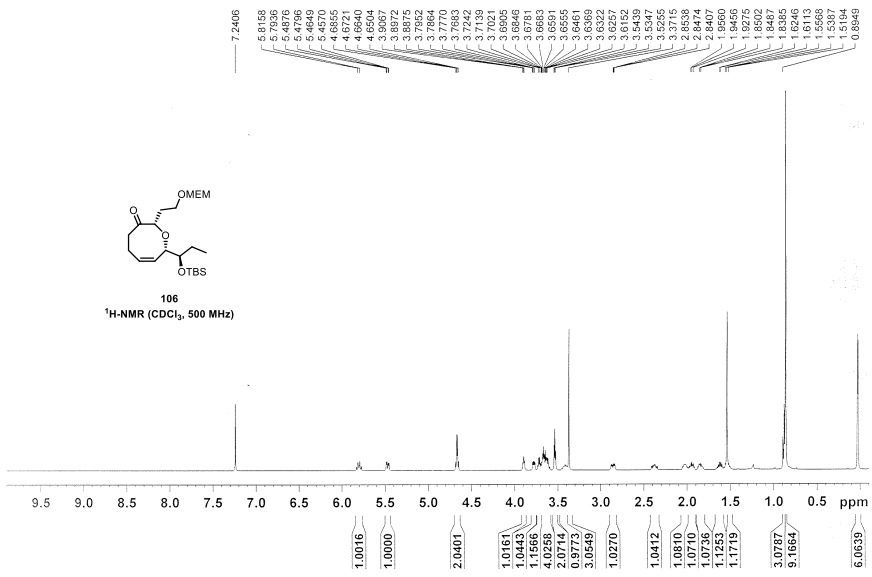

170.746
132.575
128.276
95.534
81.091
77.251
76.998
76.743
75.788
75.242
72.788
66.914
64.882
64.234
64.213
59.021
30.977
26.361
25.856
20.886
18.145
9.458
-4.236
-4.457
HO
OMEM
AcO
OTBS
105
13C-NMR (CDCl3, 125 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

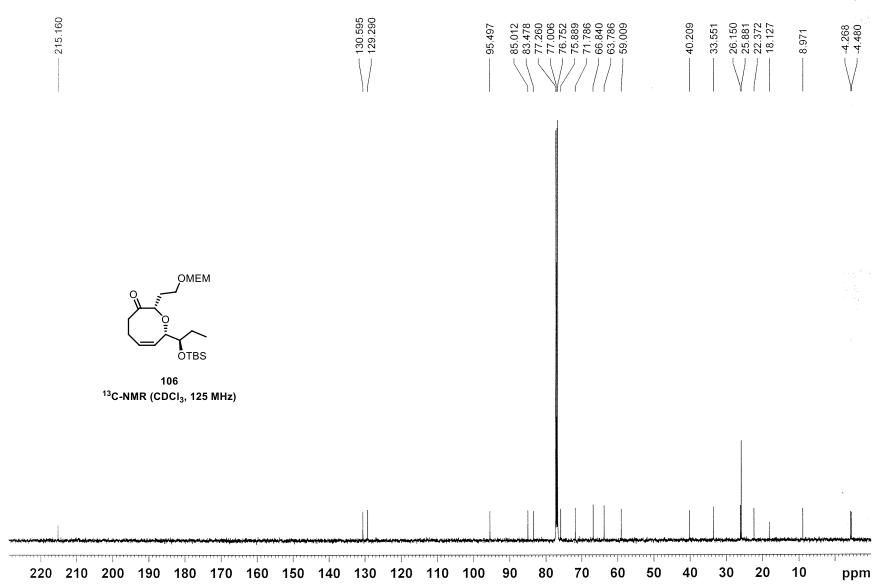

OH
PhO2S
OMEM
O
AcO
OTBS
diastereomeric mixture alcohol
1H-NMR (CDCl3, 500 MHz)
ppm

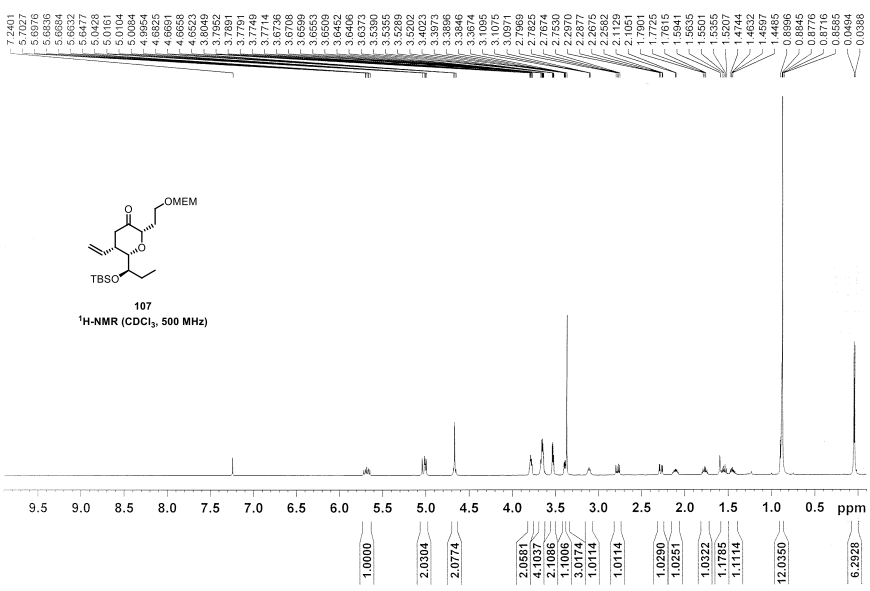

OH
PhO2S
OMEM
O
AcO
OTBS
diastereomeric mixture alcohol
13C-NMR (CDCl3, 125 MHz)
ppm

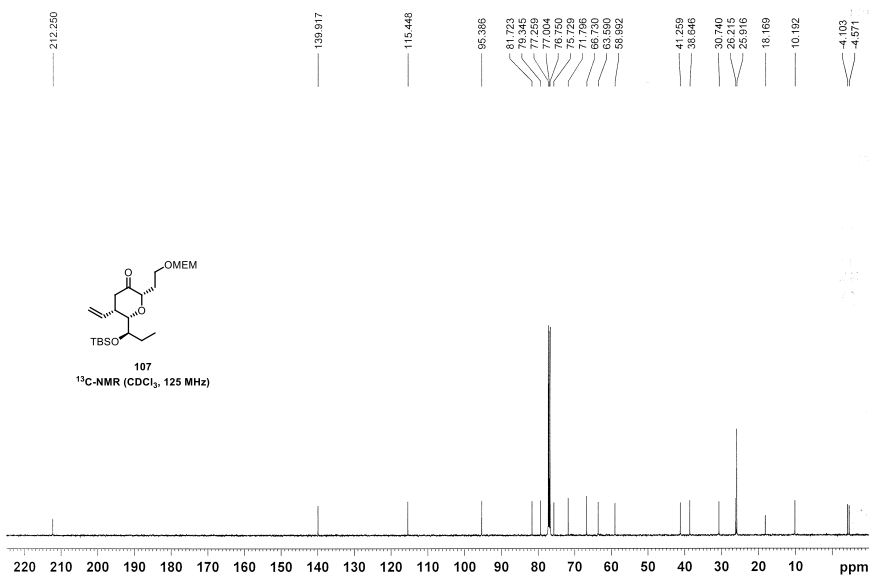

7.9228
7.9089
7.6492
7.6346
7.6194
7.5532
7.5378
7.5223
7.2464
5.7177
5.6969
5.6862
5.6754
5.6491
5.6342
5.5324
4.5165
4.5028
4.4917
4.4795
4.3969
4.3579
4.3272
4.0119
4.0004
3.9889
3.9511
3.9351
3.8496
3.8338
3.5904
3.5827
3.5740
3.5663
3.5585
3.5550
3.5443
3.5343
3.5124
3.5038
3.4946
3.3584
3.3088
2.0024
1.9873
1.9703
1.9579
1.9434
1.9073
1.8955
1.5596
1.5061
1.4937
1.4909
1.4788
1.4730
1.4635
1.4580
PhO2S
O
OMEM
AcO
OTBS
103
1H-NMR (CDCl3, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.0000
1.0299
2.0486
1.0224
1.0026
2.0562
2.0054
2.0867
1.0070
2.0906
4.1137
2.1590
3.0752
3.1009
1.1094
1.0566
2.3273
12.0575
6.2157

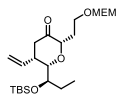

200.110
170.673
139.703
133.885
130.669
130.492
129.039
128.628
95.267
83.424
80.471
77.280
77.006
76.752
75.228
71.764
66.933
63.680
62.642
61.822
58.997
31.178
26.189
25.936
20.292
18.083
9.347
-4.191
-4.417
PhO2S
O
OMEM
AcO
OTBS
103
13C-NMR (CDCl3, 125 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.2406
5.8158
5.7936
5.4876
5.4796
5.4649
5.4570
4.6935
4.6727
4.6640
4.6504
3.9067
3.8972
3.8875
3.7952
3.7864
3.7770
3.7683
3.7242
3.7139
3.7021
3.6905
3.6846
3.6751
3.6683
3.6591
3.6555
3.6451
3.6369
3.6322
3.6257
3.6152
3.5439
3.5347
3.5255
3.3715
2.8538
2.8414
2.8407
1.9560
1.9456
1.9275
1.8502
1.8467
1.6385
1.6246
1.6113
1.5568
1.5387
1.5194
0.8949
OMEM
OTBS
106
1H-NMR (CDCl3, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0016
1.0000
2.0401
1.0161
1.0443
1.1566
4.0258
2.0714
0.9773
3.0549
1.0270
1.0412
1.0810
1.0710
1.0736
1.1253
1.1719
3.0787
9.1664
6.0639


215.160
130.595
129.290
95.497
85.012
83.478
77.260
77.006
76.752
75.689
71.786
69.640
63.786
59.009
40.209
33.551
26.150
25.881
22.372
18.127
8.971
-4.268
-4.480
OMEM
OTBS
106
13C-NMR (CDCl3, 125 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

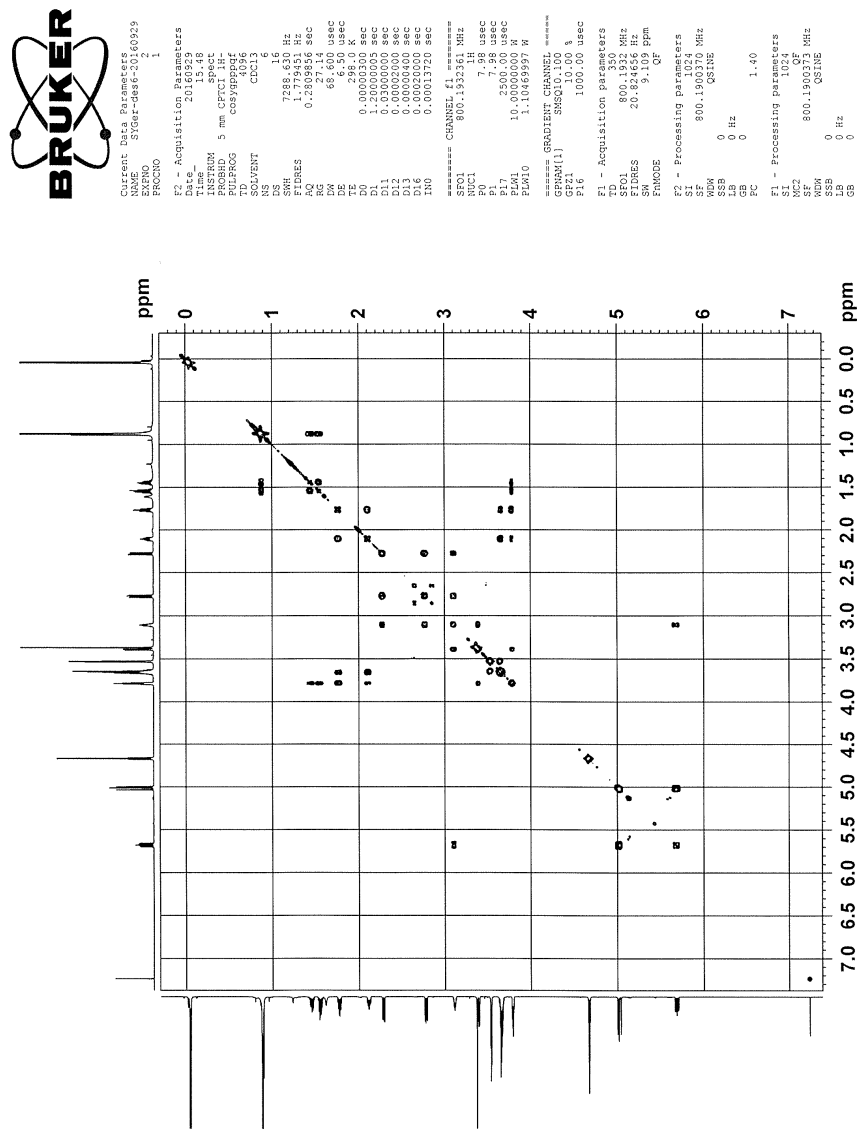

OMEM
TBSO
107
^{1}H-NMR (CDCl$_3$, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0000 2.0304 2.0774 2.0561 4.1037 2.1086 1.1006 3.0174 1.0114 1.0114 1.0290 1.0251 1.0322 1.1795 1.1114 12.0350 6.2928

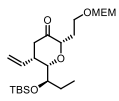

212.250
139.917
115.448
95.386
81.723
79.345
77.259
77.004
76.750
75.729
71.796
69.730
63.590
58.992
41.259
38.646
30.740
26.215
25.916
18.169
10.192
-4.103
-4.571
OMEM
TBSO
107
^{13}C-NMR (CDCl$_3$, 125 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



107

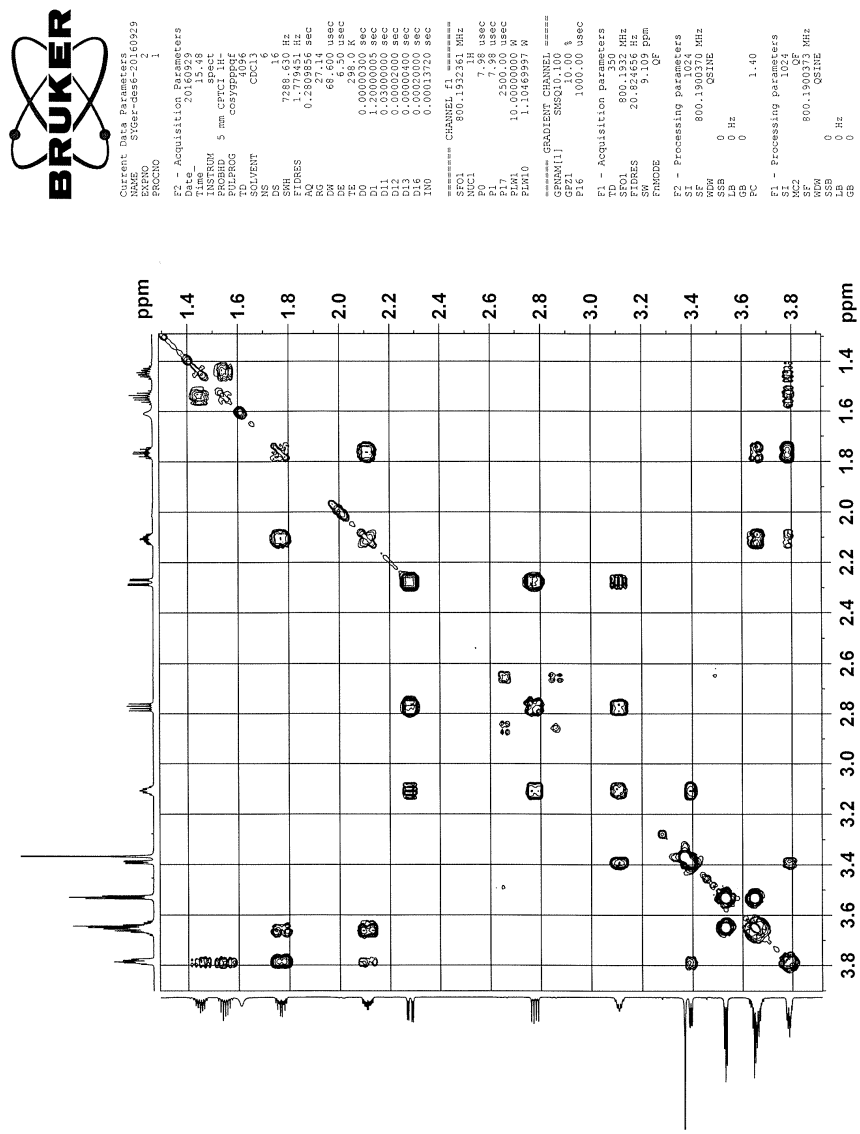
^{1}H-^{1}H COSY NMR ($CDCl_3$, 800 MHz)

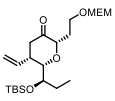




107

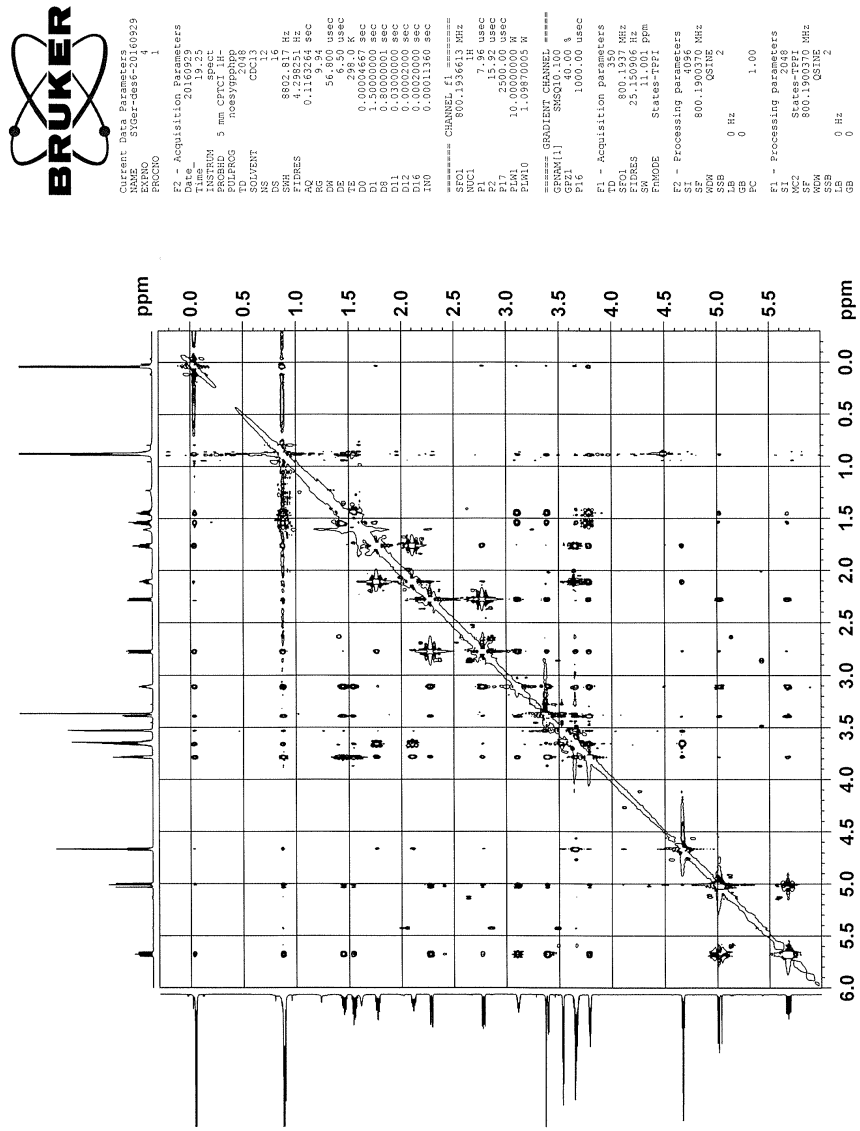
^{1}H-^{1}H COSY NMR ($CDCl_3$, 800 MHz)

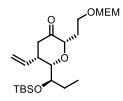




107

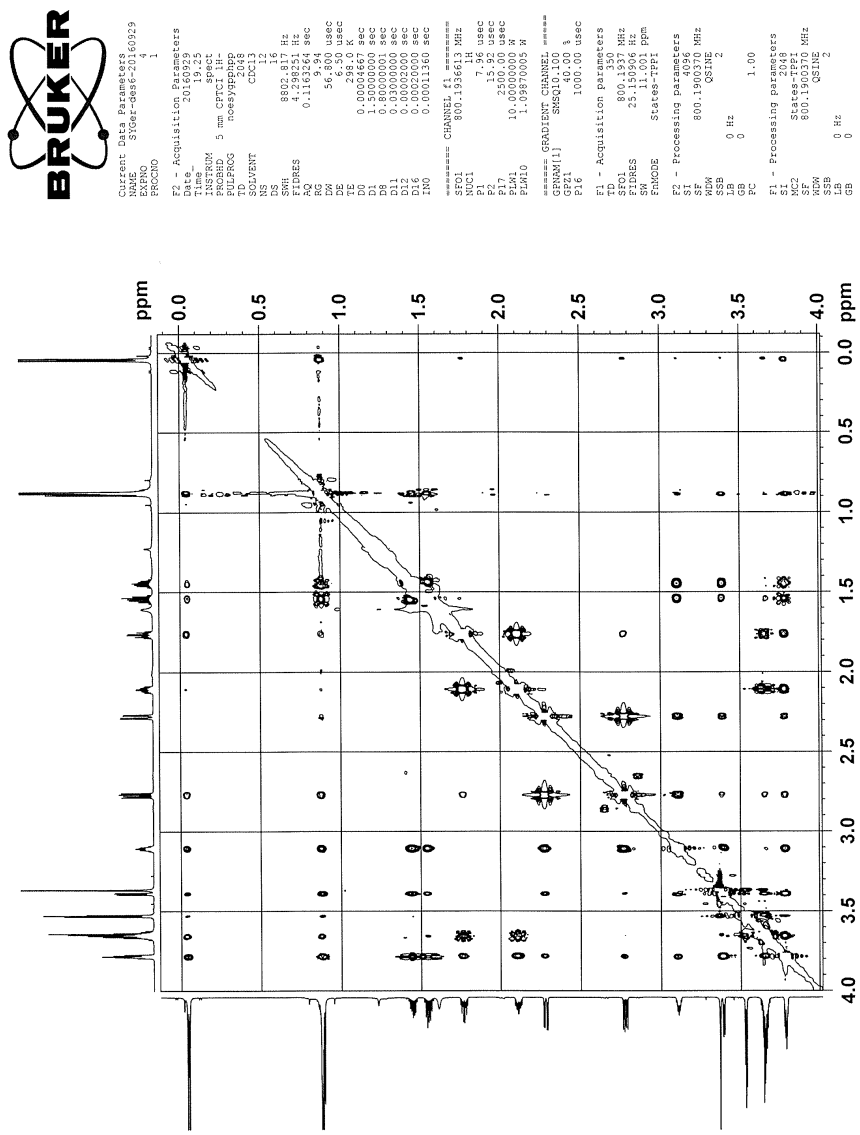
^{1}H-^{1}H NOESY NMR ($CDCl_3$, 800 MHz)

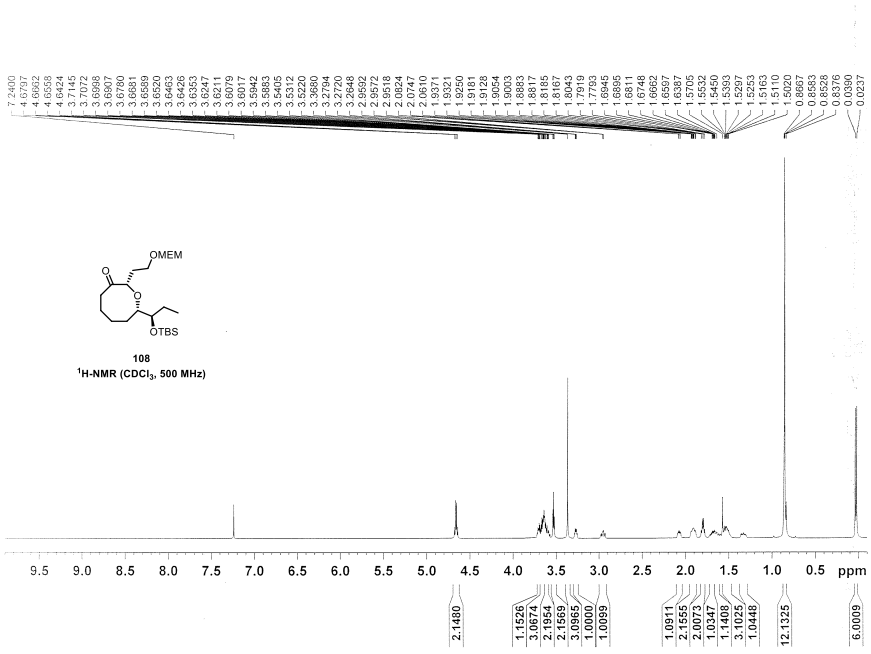


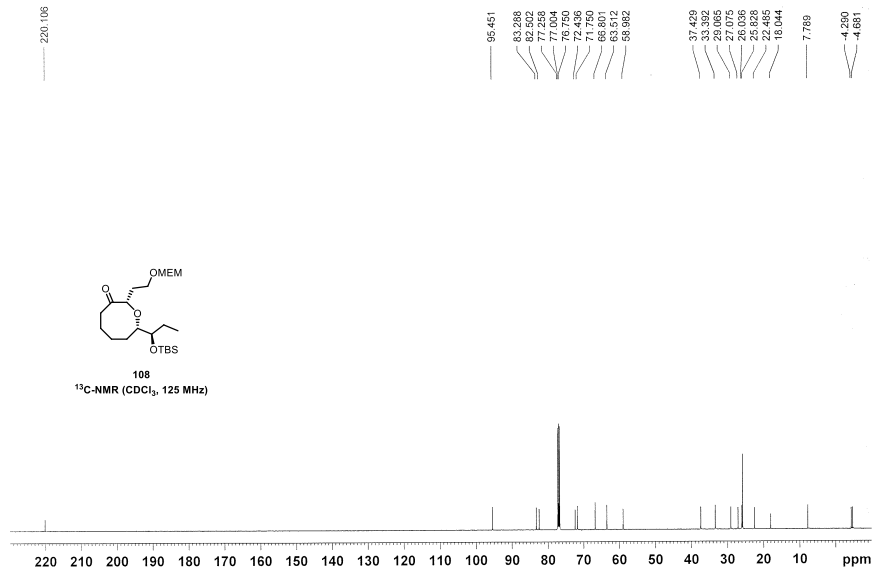


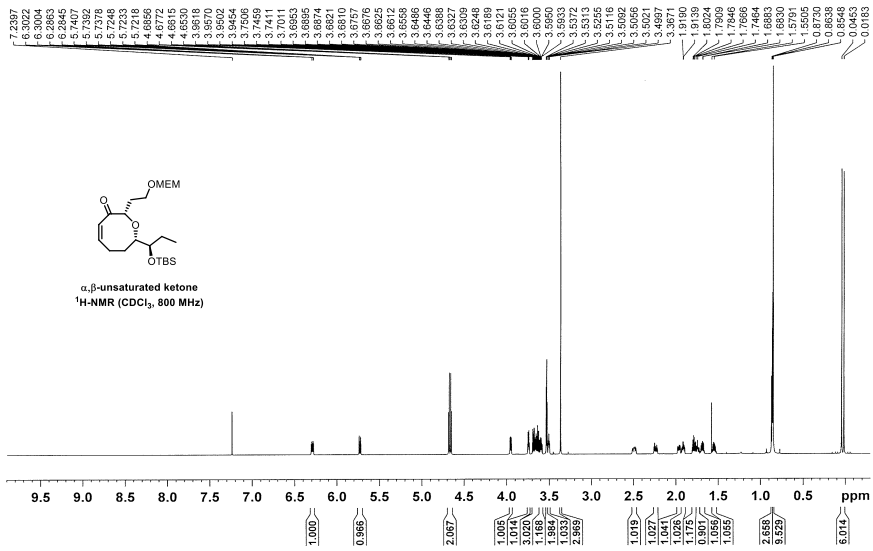
107

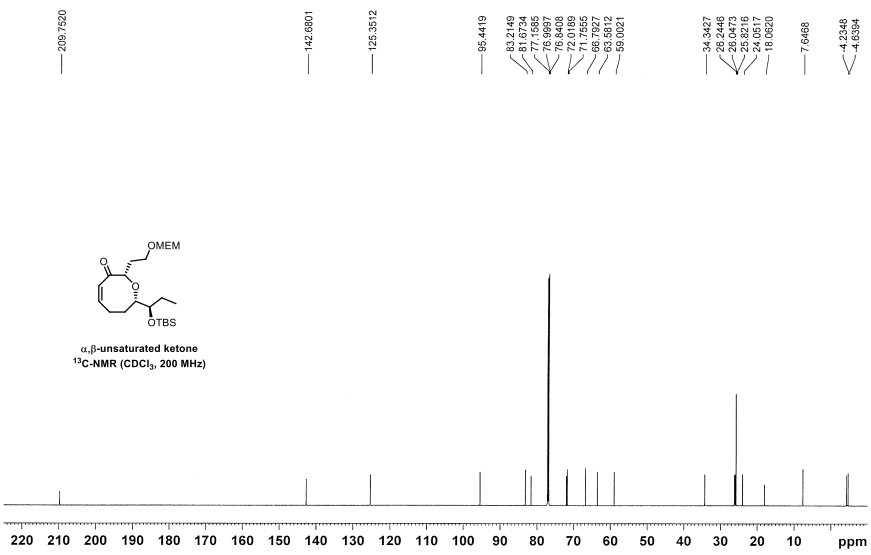
^{1}H-^{1}H NOESY NMR ($CDCl_3$, 800 MHz)

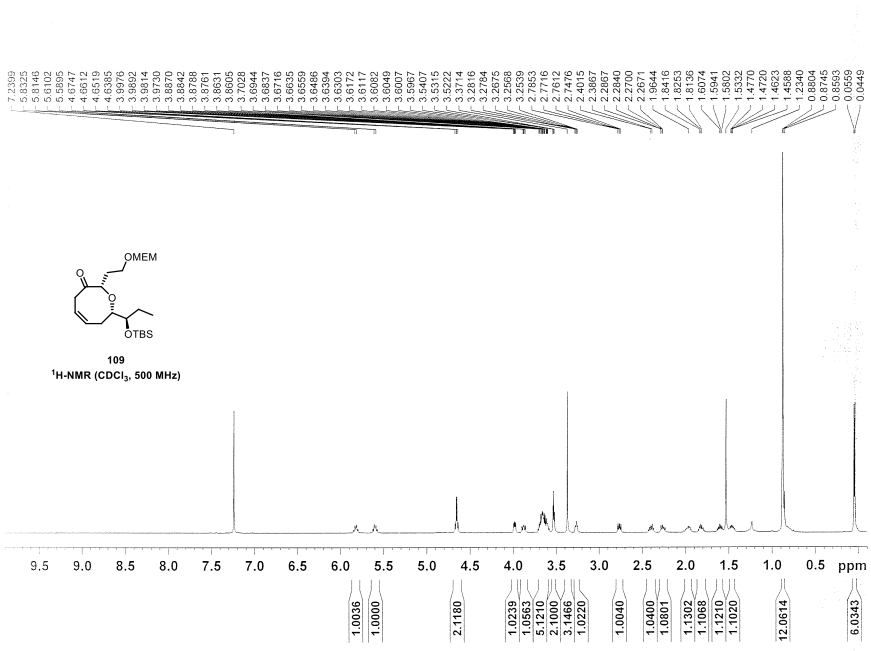


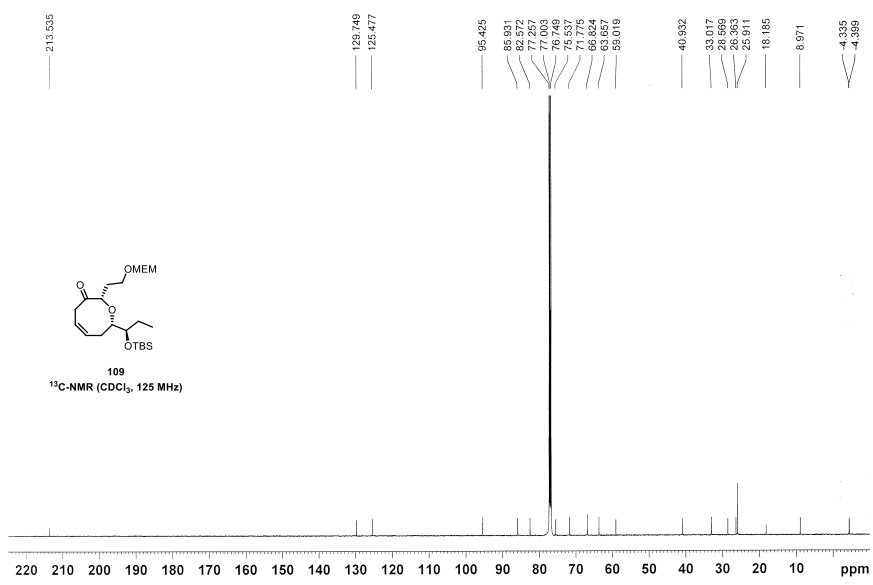

OMEM
OTBS
108
^{1}H-NMR ($CDCl_3$, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.1480
1.1526
3.0674
2.1954
2.1569
3.0965
1.0000
1.0099
1.0911
2.1555
2.0073
1.1047
1.1408
3.1025
1.0448
12.1325
6.0009

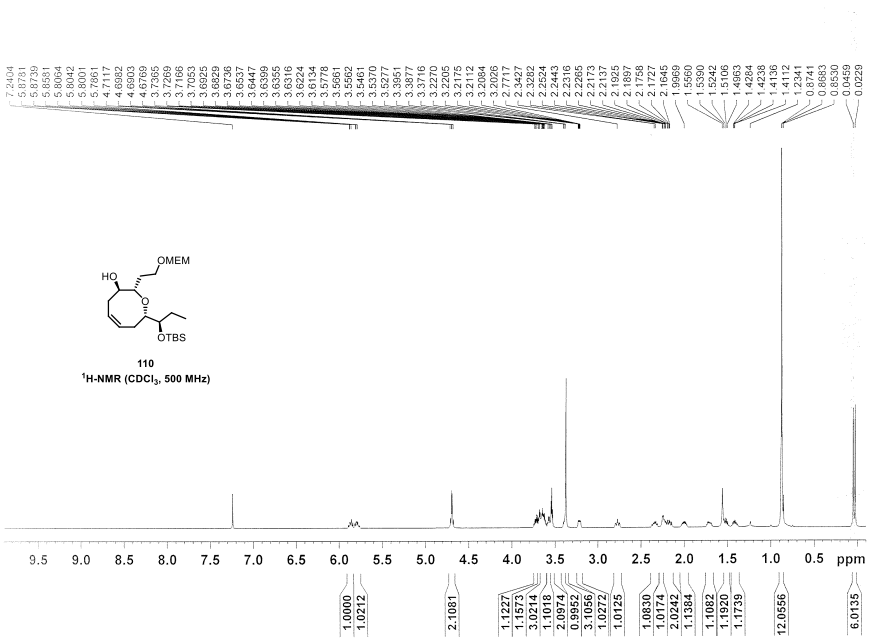

OMEM
OTBS
108
^{13}C-NMR ($CDCl_3$, 125 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

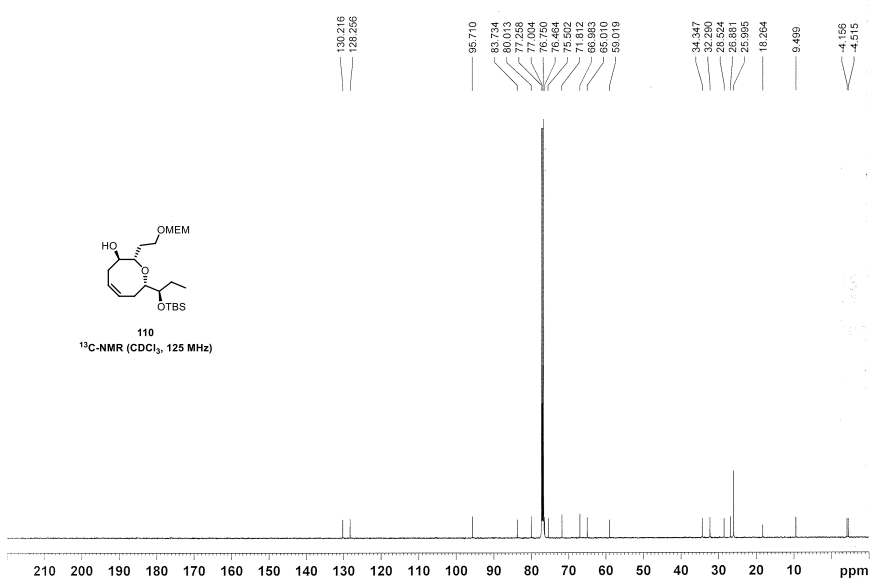

OMEM
OTBS
α,β-unsaturated ketone
^{1}H-NMR ($CDCl_3$, 800 MHz)
ppm

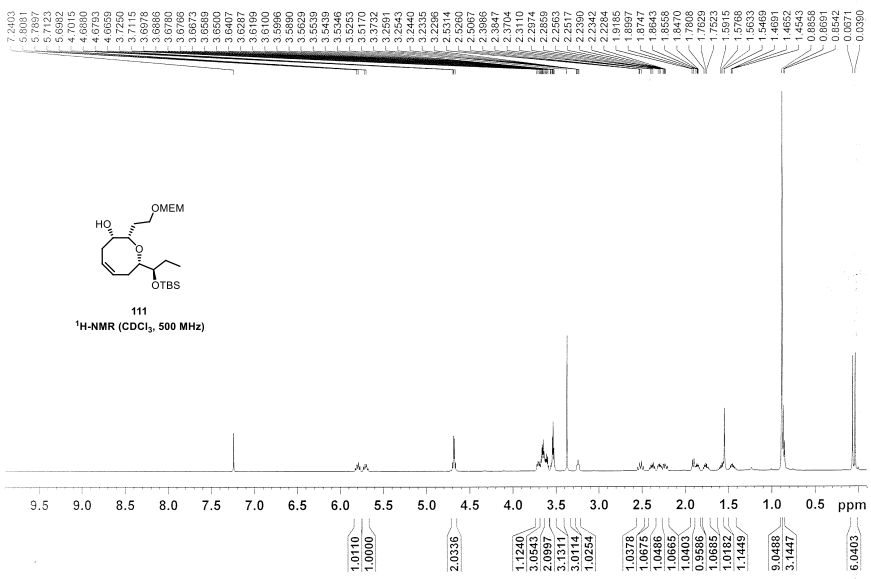

OMEM
OTBS
α,β-unsaturated ketone
^{13}C-NMR ($CDCl_3$, 200 MHz)
ppm

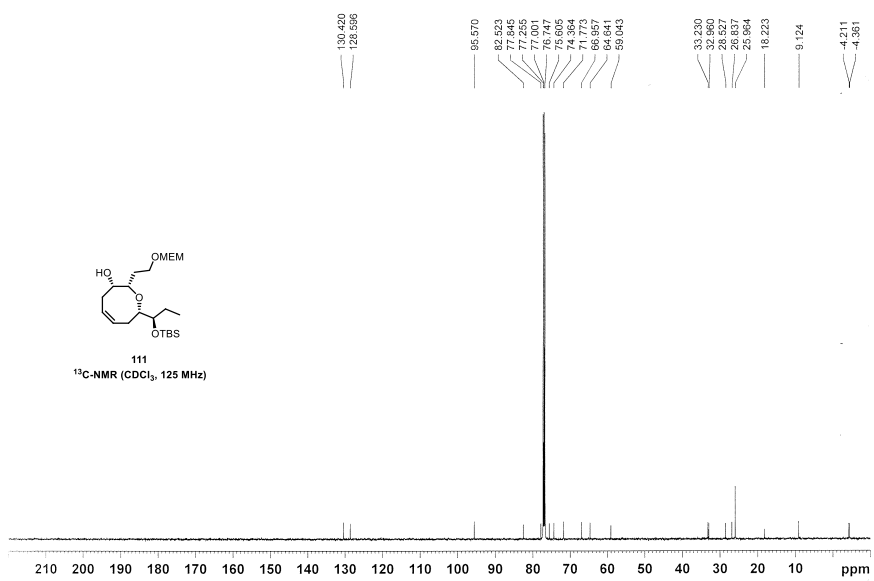

OMEM
OTBS
109
^{1}H-NMR ($CDCl_3$, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0036
1.0000
2.1180
1.0239
1.0563
5.1210
2.1000
3.1466
1.0220
1.0040
1.0400
1.0801
1.1302
1.1068
1.1210
1.1020
12.0614
6.0343

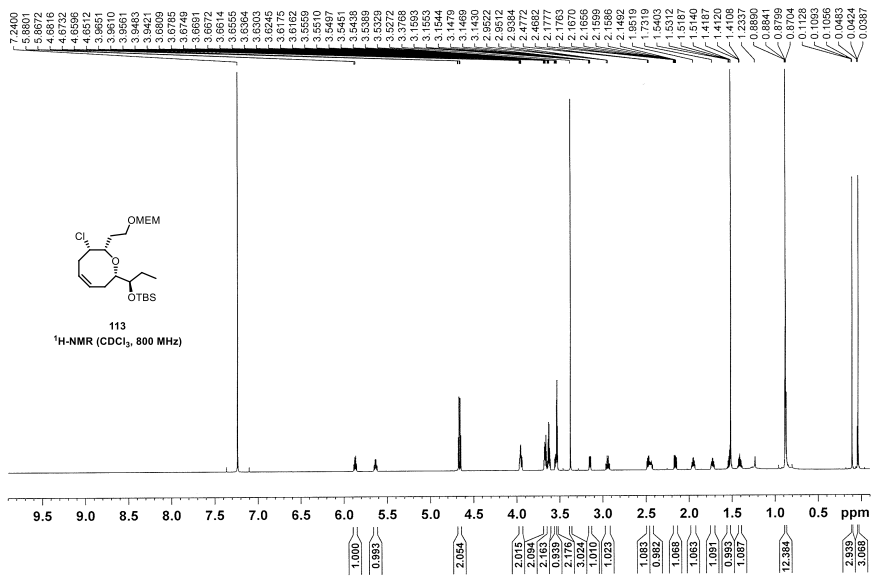

213.535
129.749
125.477
95.425
85.931
82.572
77.257
77.003
76.749
75.537
71.775
66.824
63.657
59.019
40.932
33.017
28.569
26.363
25.911
18.185
8.971
-4.335
-4.399
OMEM
OTBS
109
^{13}C-NMR ($CDCl_3$, 125 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


OMEM
HO
O
OTBS
110
^{1}H-NMR (CDCl$_3$, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


OMEM
HO
O
OTBS
110
^{13}C-NMR (CDCl$_3$, 125 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

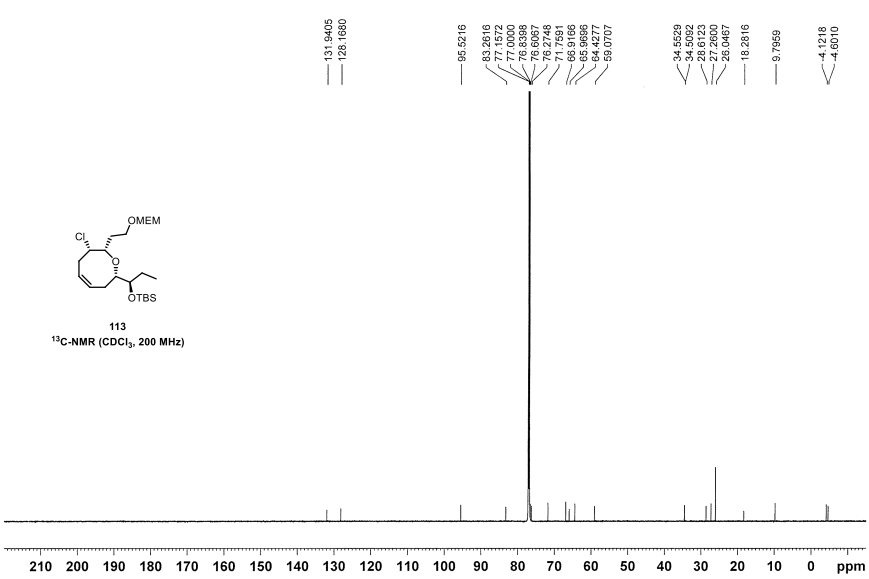

OMEM
HO
O
OTBS
111
^{1}H-NMR ($CDCl_3$, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0110
1.0000
2.0336
1.1240
3.0543
2.0997
3.1311
3.0114
1.0254
1.0378
1.0675
1.0486
1.0665
1.0403
0.9586
1.0685
1.0182
1.1449
9.0488
3.1447
6.0403


130.420
128.596
95.570
82.523
77.845
77.255
77.001
76.747
75.605
74.364
71.773
66.957
64.841
59.043
33.230
31.960
28.837
26.837
25.964
18.223
9.124
-4.211
-4.361
OMEM
HO
O
OTBS
111
^{13}C-NMR ($CDCl_3$, 125 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



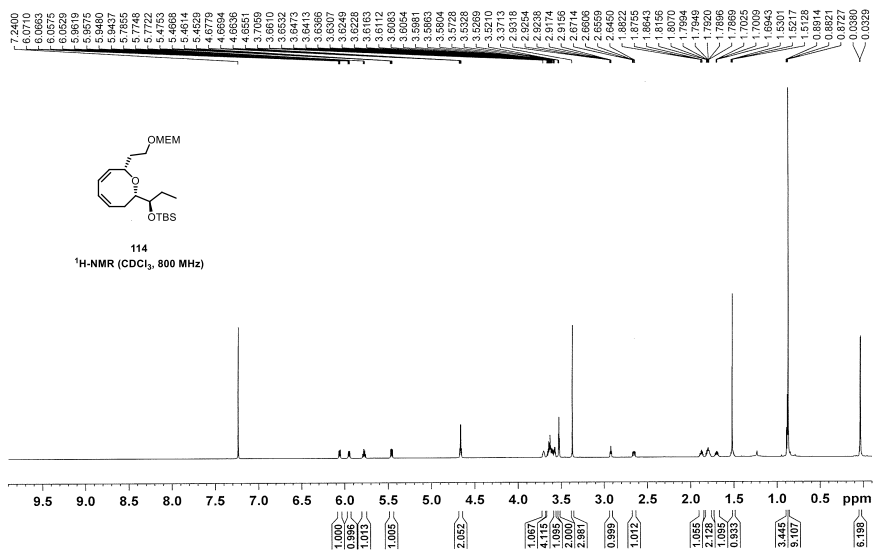
113

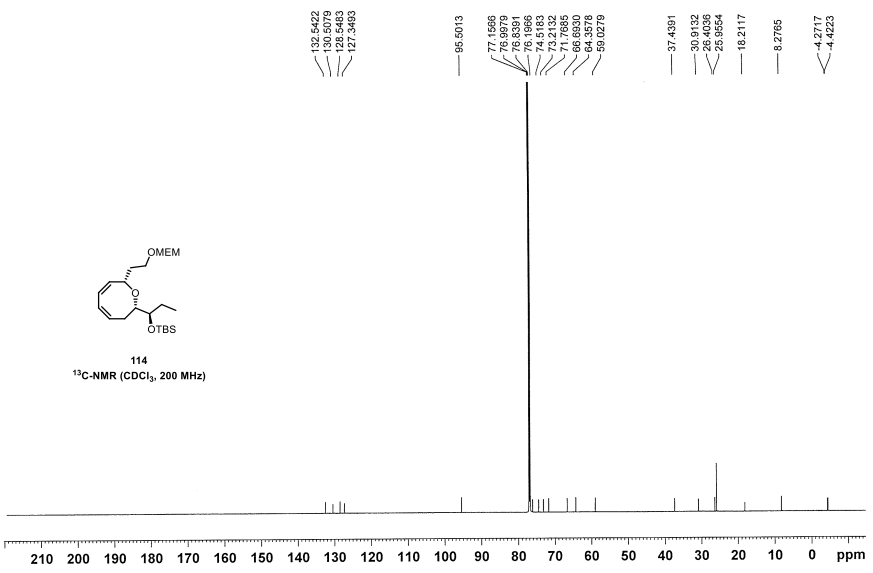
^{1}H-NMR ($CDCl_3$, 800 MHz)

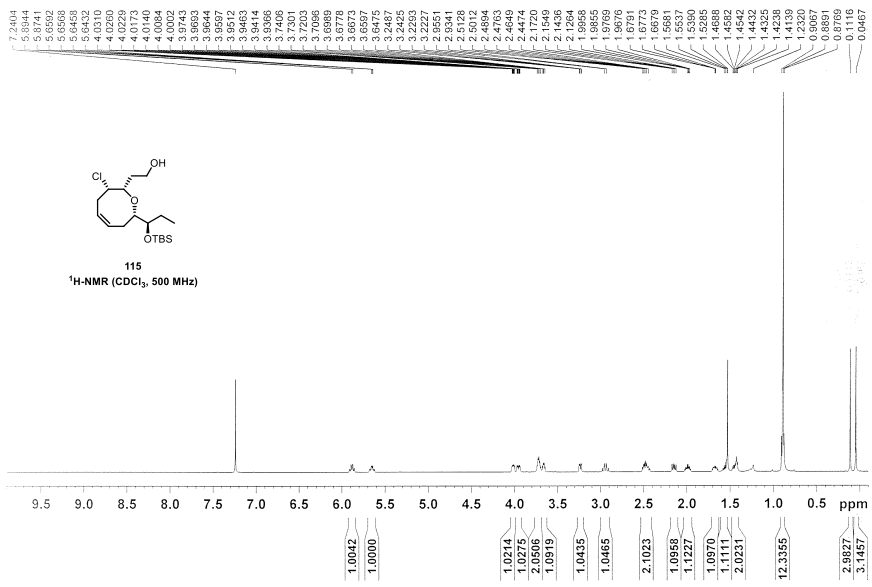


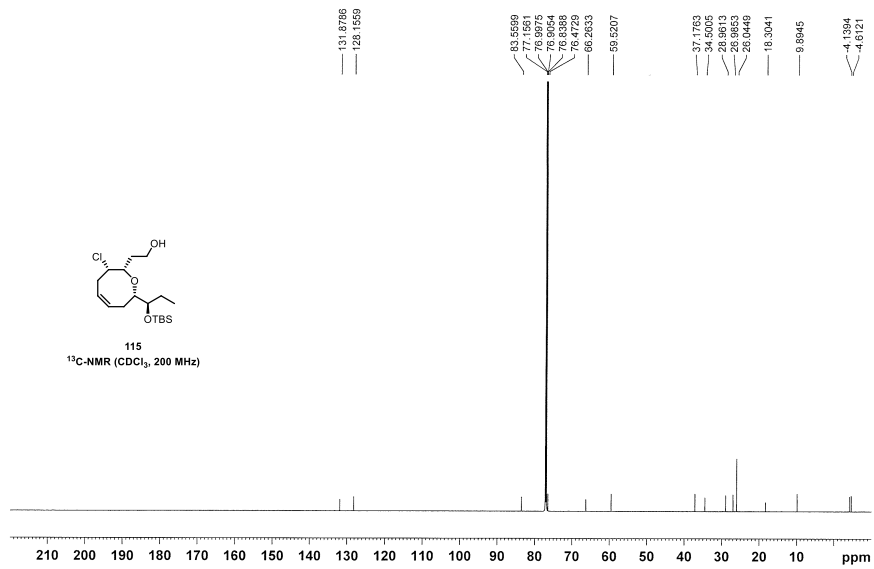
113

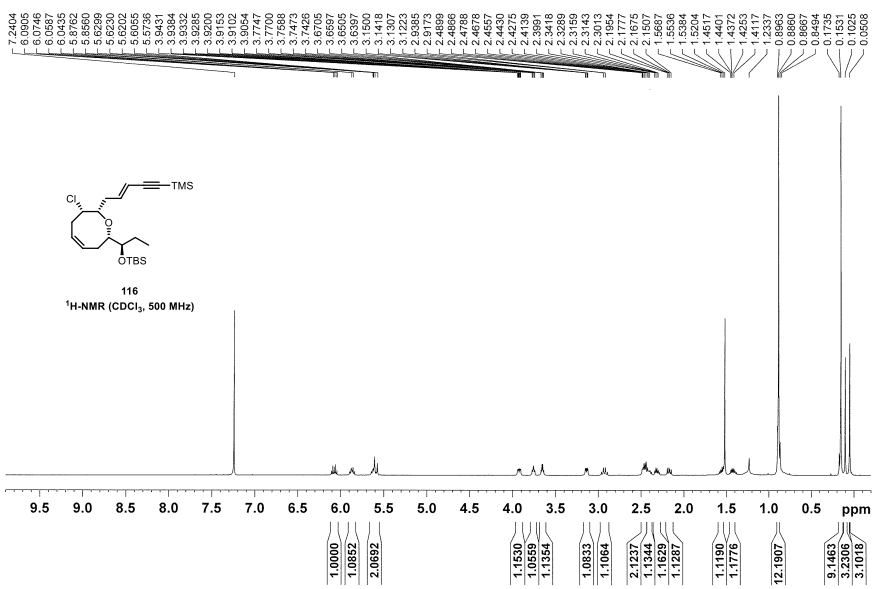
^{13}C-NMR ($CDCl_3$, 200 MHz)

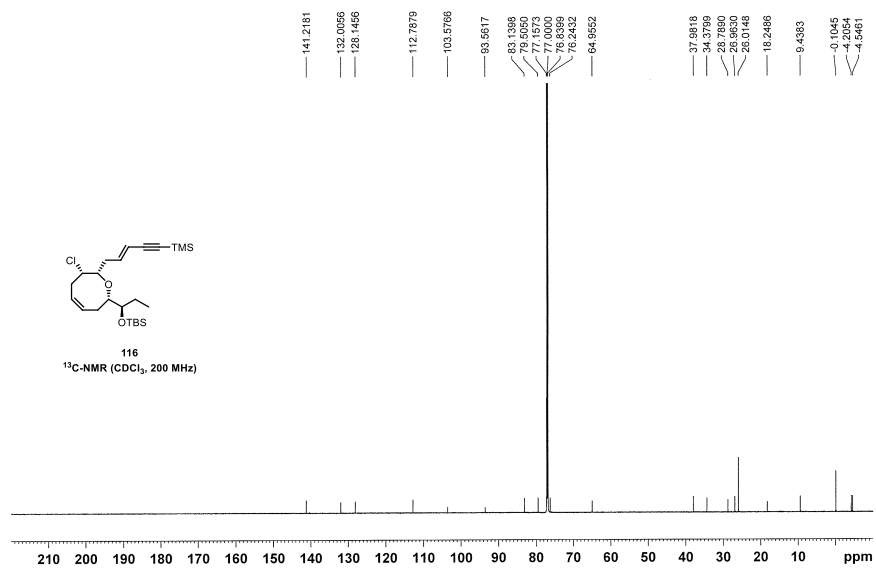

OMEM
OTBS
114
^{1}H-NMR ($CDCl_3$, 800 MHz)
ppm

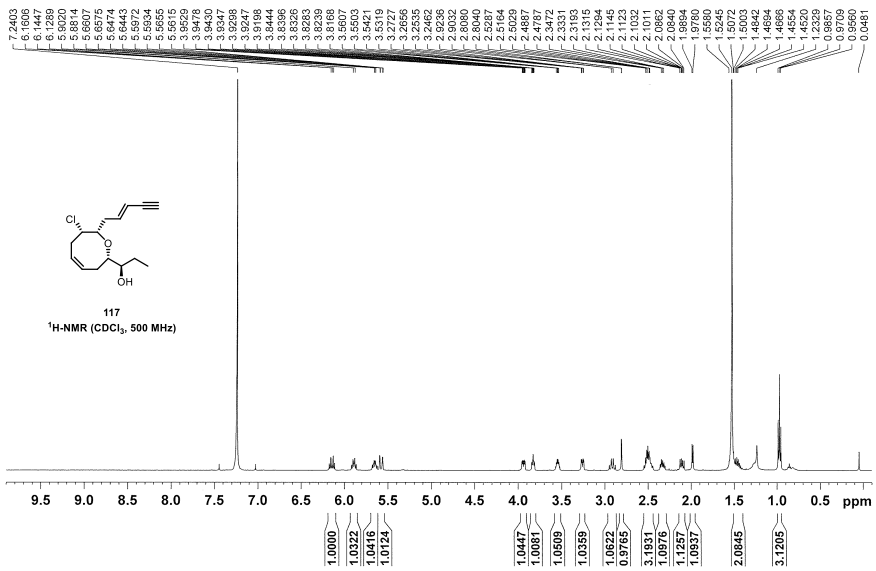

OMEM
OTBS
114
^{13}C-NMR ($CDCl_3$, 200 MHz)
ppm


OH
Cl
O
OTBS
115
^{1}H-NMR (CDCl$_3$, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0042
1.0000
1.0214
1.0275
2.0506
1.0919
1.0435
1.0465
2.1023
1.0958
1.1227
1.0970
1.1111
2.0231
12.3355
2.9827
3.1457

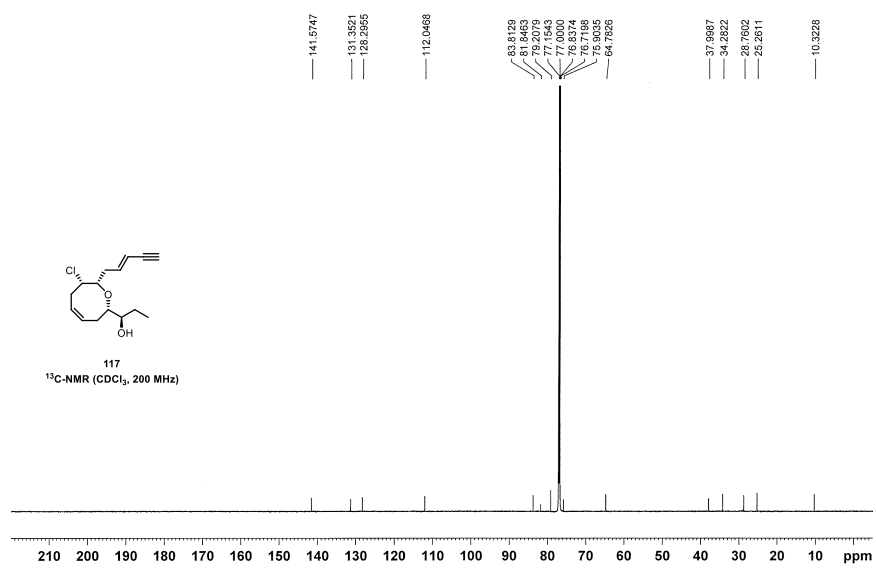

131.8786
128.1559
83.5599
77.3581
76.9975
76.8054
76.6388
76.4729
66.2633
59.5207
37.1763
34.5005
28.9613
28.9853
26.0449
18.3041
9.8945
-4.1394
-4.6121
OH
Cl
O
OTBS
115
^{13}C-NMR (CDCl$_3$, 200 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


TMS
Cl
O
OTBS
116
^{1}H-NMR ($CDCl_3$, 500 MHz)
ppm
1.0000
1.0852
2.0692
1.1530
1.0559
1.1354
1.0833
1.1064
2.1237
1.1344
1.1629
1.1287
1.1190
1.1776
12.1907
9.1463
3.2306
3.1018

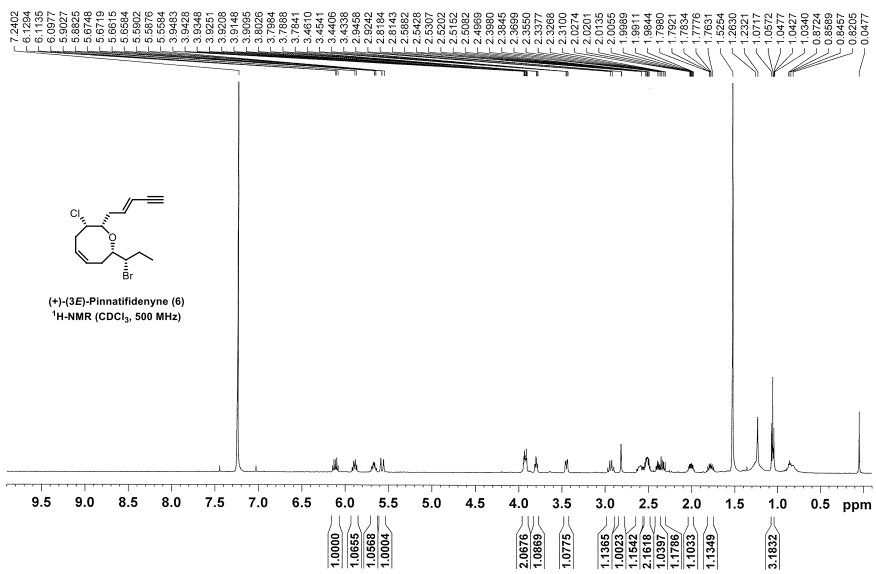

TMS
Cl
O
OTBS
116
^{13}C-NMR ($CDCl_3$, 200 MHz)
ppm

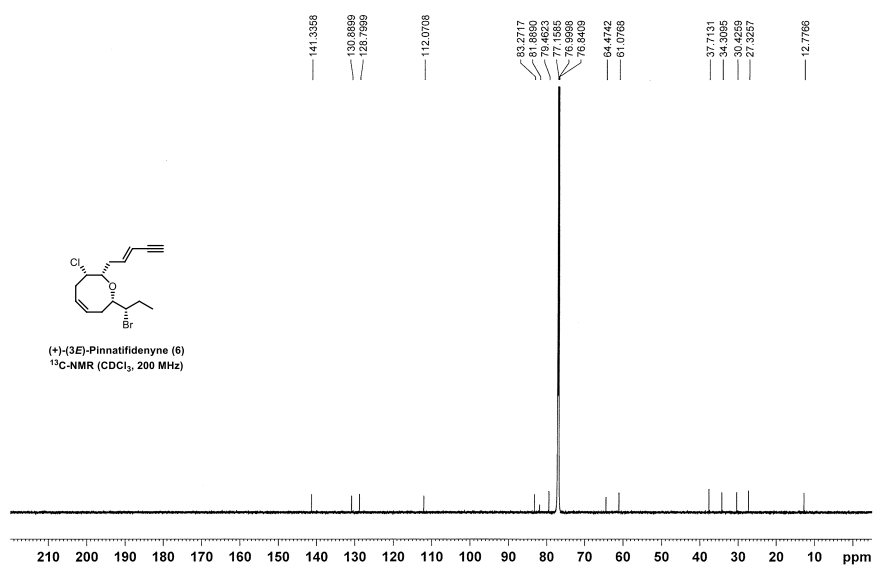


117
^{1}H-NMR ($CDCl_3$, 500 MHz)



117
^{13}C-NMR ($CDCl_3$, 200 MHz)


(+)-(3E)-Pinnatifidenyne (6)
1H-NMR (CDCl3, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0000 1.0655 1.0568 1.0004 2.0676 1.0869 1.0775 1.1365 1.0023 1.1542 2.1618 1.0397 1.1786 1.1033 1.1349 3.1832


(+)-(3E)-Pinnatifidenyne (6)
13C-NMR (CDCl3, 200 MHz)
141.3358 130.8899 128.7999 112.0708 83.2717 81.8690 79.4623 77.1566 76.8998 76.8409 64.4742 61.0768 37.7131 34.3095 30.4259 27.3257 12.7766
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

VII. Abstract in Korean

홍조류인 *Laurencia* 종은 1개 이상의 할로젠 원소, 다양한 입체 구조 및 곁사슬기를 가지는 중간 고리 할로 ether 천연물을 형성한다고 알려져 있으며, 1965년 T. Irie 연구팀에 의해 (+)-Laurencin 이 최초로 분리, 보고된 이후 최근까지 중간 고리 ether 를 중심 골격으로 갖는 다양한 해양 천연물들이 보고되고 있다. 이러한 2차 대사 물질들은 생물학적 활성 뿐 아니라, 열역학적으로 선호되지 않아 합성적으로 접근하기 어려운 8-고리 ether 의 구조적 특징으로 인해 많은 합성 연구팀들의 관심을 집중시키고 있으며, 현재도 그와 관련한 연구들이 활발히 진행되고 있다.

본 연구진은 통합적 합성 방법을 바탕으로 (+)-(3*E*)-Pinnatifidenyne 의 입체 선택적 전합성을 진행하였다. 본 합성에서는 높은 위치 선택성을 가지는 분자 내 Tsuji-Trost 알릴화 반응 및 비접합 이성질화 반응을 통해 효율적으로 *cis*-α,α'-이중치환 8-고리 ether 중심 구조를 구축하였으며, 기질을 바탕으로 부분 입체 선택적 환원 반응을 이용하여 중요한 chloride 를 도입함으로써 최종적으로 전합성을 마무리 하였다. 이를 바탕으로 현재 Pd 촉매 하의 고리화 반응의 전구체를 효율적으로 합성하기 위하여 Lewis 산을 매개로 epoxide 개열 반응을 통한 수렴적 합성 전략을 구축하고 있으며, 이러한 통합적 합성 방법은 다른 *Laurencia* 종으로부터 유래된 보다 독특하고 복잡한 형태를 가진 8-고리 ether 천연물의 합성에 적용할 수 있을 것으로 기대하고 있다.

주요어 : 중간 고리 할로ether, *Laurencia* 종, Pinnatifidenyne, *cis*-α,α'-이중치환 8-고리 ether, 분자내 Tsuji-Trost 알릴화 반응, 비접합 이성질화 반응

학번 : 2012-30457